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(54) Title: **BIOLOGICALLY ABSORBABLE COATINGS FOR IMPLANTABLE DEVICES BASED ON COPOLYMERS HAVING ESTER BONDS AND METHODS FOR FABRICATING THE SAME**

(57) Abstract: Coatings for an implantable medical device and a method of fabricating thereof are disclosed, and the coatings comprise biologically absorbable poly(ester amides).

BIOLOGICALLY ABSORBABLE COATINGS FOR IMPLANTABLE DEVICES BASED ON  
COPOLYMERS HAVING ESTER BONDS AND METHODS FOR FABRICATING THE  
SAME

5

BACKGROUND

1. Field of the Invention

This invention is directed to coatings for drug delivery devices, such as drug eluting vascular stents, and methods for producing the same.

10 2. Description of the State of the Art

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the  
15 occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially compress against the atherosclerotic plaque of the lesion to remodel the lumen wall. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of intimal flaps or  
20 torn arterial linings which can collapse and occlude the conduit after the balloon is deflated. Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may require another angioplasty procedure or a surgical by-pass operation. To

reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, a stent is implanted in the lumen to maintain the vascular patency.

Stents are used not only as a mechanical intervention but also as a vehicle for providing biological therapy. As a mechanical intervention, stents act as scaffoldings, functioning to physically hold open and, if desired, to expand the wall of the passageway. Typically, stents are capable of being compressed, so that they can be inserted through small vessels via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in patent literature disclosing stents which have been applied in PTCA procedures include stents illustrated in U.S. Patent No. 4,733,665 issued to Palmaz, U.S. Patent No. 4,800,882 issued to Gianturco, and U.S. Patent No. 4,886,062 issued to Wiktor.

Biological therapy can be achieved by medicating the stents. Medicated stents provide for the local administration of a therapeutic substance at the diseased site. In order to provide an efficacious concentration to the treated site, systemic administration of such medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. Local delivery thus produces fewer side effects and achieves more favorable results. One proposed method for medicating stents involves the use of a polymeric carrier coated onto the surface of a stent. A solution which includes a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent. The solvent is allowed to evaporate, leaving on the stent surface a coating of the polymer and the therapeutic substance impregnated in the polymer.

One polymer that can be used for making stent coatings for local drug delivery can be selected from a group of poly(ester amides) described in U.S. Patent No. 6,503,538 to Chu et al.

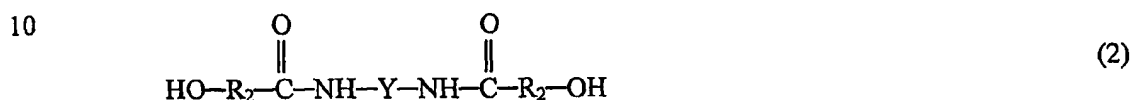
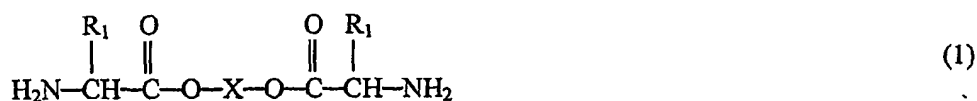
However, some properties of the poly(ester amides) taught by Chu et al. may be insufficiently good for drug-eluting stent applications. For example, the drug permeabilities only encompass a certain range for these hydrophobic polymers. Additionally, the biocompatibility of poly(ester amides) with hydrophilic, non-fouling moieties can be greater than those without. Accordingly,

5 there is a need to have poly(ester amides) with better properties to allow the poly(ester amides) to be used in stent coatings for local drug delivery.

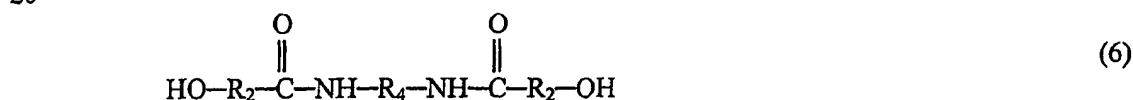
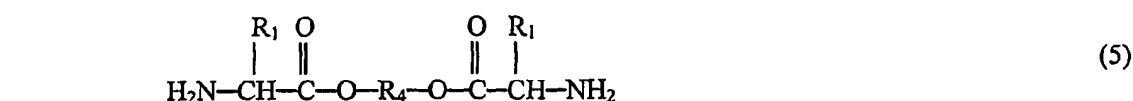
## SUMMARY

According to one aspect of the present invention, a medical article is provided, the article comprises an implantable substrate having a coating, the coating includes a polymeric product of a reaction between a first reagent, a second reagent, and a third reagent, wherein: (a) the first

5 reagent can be one of the compounds having formulae (1), (2), (3), and (4);



(b) the second reagent can be one of the compounds having formulae (5), (6), (7), and (8);



and, (c) the third reagent can be a dicarboxylic acid having the formula (9):



In formulae (1)-(9), R<sub>1</sub> can be hydrogen, methyl, *iso*-propyl, *sec*-butyl; *iso*-butyl, or benzyl group; R<sub>2</sub> can be methylene, methylenemethylene, *n*-propylene, *iso*-propylene, ethylmethylene, *n*-butylene, *iso*-butylene, *sec*-butylene, or *n*-amylene group; R<sub>3</sub> can be a straight chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is an integer between 2 and 12; R<sub>4</sub> can be a moiety derived from a compound selected from a group consisting of poly(ethylene glycol), poly(propylene glycol), random poly(ethylene glycol-co-propylene glycol), poly(ethylene glycol)-block-poly(propylene glycol), hyaluronic acid, poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropylmethacrylamide), poly(styrene sulfonate), poly(vinyl pyrrolidone), and cellulose; X can be a straight chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is an integer between 2 and 12; and Y can be a straight chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is 1, 2, or 5.

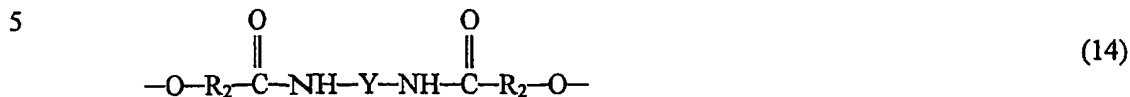
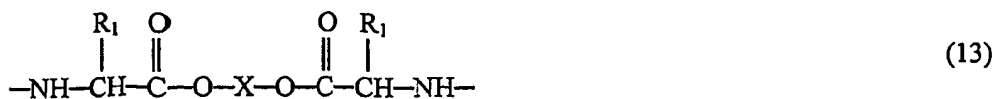
According to another aspect of the present invention, a medical article is provided, the article comprises an implantable substrate having a coating, the coating including a copolymer having a general formula (10) or (11):



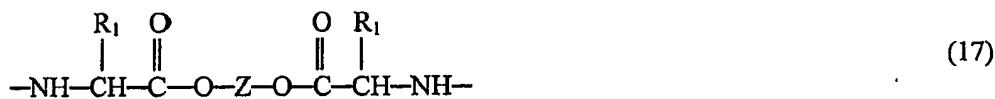
wherein, M can be a moiety represented by the structure having the formula (12);



P can be one of the moieties having the formulae (13), (14), (15), and (16);



Q can be one of the moieties having the formulae (17), (18), and (19);



and M<sub>1</sub> can be a moiety represented by the formula (20);



In formulae (10)-(20), R<sub>1</sub> can be hydrogen, methyl, *iso*-propyl, *sec*-butyl, *iso*-butyl, or benzyl group; R<sub>2</sub> can be methylene, methylenemethylene, *n*-propylene, *iso*-propylene, ethylenemethylene, *n*-butylene, *iso*-butylene, *sec*-butylene, or *n*-amylene group; R<sub>3</sub> can be a straight  
 30 chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is an integer between 2 and 12; X can be a straight chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is an integer between 2 and 12; Y can be a straight chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is 1, 2, or 5; Z can be a moiety derived from a compound selected from a group

consisting of poly(ethylene glycol), poly(propylene glycol), random poly(ethylene glycol-co-propylene glycol), poly(ethylene glycol)-block-poly(propylene glycol), hyaluronic acid, poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropylmethacrylamide), poly(styrene sulfonate), poly(vinyl pyrrolidone), and cellulotics; and m, n, and p can be integers where the value of m is  
5 between 5 and 1,800, the value of n is between 1 and 800 and the value of p is between 4 and 1,500.

According to yet another aspect of the current invention, a method for fabricating a medical article is provided, the method includes synthesizing a copolymer and forming a coating based on the copolymer on at least a portion of an implantable substrate, the synthesizing of the  
10 copolymer including reacting a first reagent with a second reagent and with a third reagent, wherein: (a) the first reagent can be one of the compounds having formulae (1), (2), (3), and (4); (b) the second reagent can be one of the compounds having formulae (5), (6), (7), and (8); and (c) the third reagent is a dicarboxylic acid having the formula (9), where the formulae (1)-(9) are provided above.

15 According to yet another aspect of the current invention, a method for fabricating a medical article is provided, the method including synthesizing a copolymer and forming a coating based on the copolymer on at least a portion of an implantable substrate, wherein the copolymer has a general formula (10) or (11), where the formulae (10) and (11) are provided above.



## DETAILED DESCRIPTION

1. Terms and Definitions.

The following definitions apply:

- The term “biologically absorbable” coatings and/or polymers is defined as coatings  
5 and/or polymers that are capable of being completely degraded and/or eroded when exposed to  
bodily fluids such as blood and are gradually resorbed, absorbed and/or eliminated by the body.  
The processes of breaking down and eventual absorption and elimination of the coating and/or  
polymer can be caused, for example, by hydrolysis, metabolic processes, bulk or surface erosion,  
and the like.
- 10 Whenever the reference is made to “biologically absorbable” stent coatings and/or  
polymers forming such stent coatings, it is understood that after the process of degradation,  
erosion, absorption, and/or resorption has been completed, no coating, in excess of possibly  
insignificant trace amount, will remain on the stent. In other words, stent coatings and/or  
polymers forming such stent coatings are considered “biologically absorbable” if the coatings  
15 and/or polymers are substantially broken down by the *in vivo* environment, or by the *in vitro*  
environment, such as one having physical, chemical, and/or biological characteristics  
substantially similar to those of the *in vivo* environment. An amount of time needed to break  
down the coatings and/or polymers can be between about 1 day and several years, or between  
about 1 day and about 24 months; alternatively, between about 2 months and about 18 months;  
20 alternatively, between about 3 month and about 12 months.

For purposes of the present invention, “substantially broken down” means that a  
substantial reduction of the molecular weight of a polymer occurs as a result of the exposure of  
the polymer to the *in vivo* environment or to a simulated *in vivo* environment. The simulated *in*

*vivo* environment can be the *in vitro* environment having physical, chemical, and/or biological characteristics that are identical or substantially similar to those of the *in vivo* environment.

Standard analytical techniques normally used by those having ordinary skill in the art can be used to monitor the change of the molecular weight of the polymer. One analytical technique that can be used includes immersing the polymer in a simulated *in vivo* environment and measuring the loss of the molecular weight of the polymer over time. A number of methods can be used for measuring the molecular weight, for example, gel permeation chromatography (GPC). In some embodiments, if the polymer has lost more than about 10 % of its original molecular weight over a 3-month period, then it can be classified as biodegradable.

The term "poly(ester amide)" or "PEA" is defined as a polymer having both at least one ester bond (I) and at least one amide bond (II):



## 2. Embodiments of the Invention.

A coating for an implantable medical device, such as a stent, according to embodiments of the present invention, can be a multi-layer structure that can include the following three layers:

(a) a drug-polymer layer (also referred to as "reservoir" or "reservoir layer"), comprising a polymer and a drug, or alternatively a polymer free drug layer;

(b) an optional primer layer; and/or

(c) an optional topcoat layer.

Each layer of the stent coating can be formed on the stent by dissolving a polymer or a blend of polymers in a solvent, or a mixture of solvents, and applying the resulting polymer solution on the stent by spraying or immersing the stent in the solution. After the solution has been applied onto the stent, the coating is dried by allowing the solvent to evaporate. The  
5 process of drying can be accelerated if the drying is conducted at an elevated temperature.

To incorporate a drug into the reservoir layer, the drug can be combined with the polymer solution that is applied onto the stent as described above. Alternatively, to fabricate a polymer-free drug layer, the drug can be dissolved in a suitable solvent or mixture of solvents, and the resulting drug solution can be applied on the stent by spraying or immersing the stent in the drug  
10 solution.

Instead of introducing the drug as a solution, the drug can be introduced as a colloid system, such as a suspension in an appropriate solvent phase. To make the suspension, the drug can be dispersed in the solvent phase using conventional techniques used in colloid chemistry. Depending on a variety of factors, e.g., the nature of the drug, those having ordinary skill in the  
15 art can select the solvent to form the solvent phase of the suspension, as well as the quantity of the drug to be dispersed in the solvent phase. The suspension can be mixed with a polymer solution and the mixture can be applied on the stent as described above. Alternatively, the drug suspension can be applied on the stent without being mixed with the polymer solution.

The drug-polymer layer can be applied directly onto at least a part of the stent surface to  
20 serve as a reservoir for at least one active agent or a drug which is incorporated into the reservoir layer. The optional primer layer can be applied between the stent and the reservoir to improve the adhesion of the drug-polymer layer to the stent. The optional topcoat layer can be applied over at least a portion of the reservoir layer and to serve as a rate limiting membrane which helps

to control the rate of release of the drug. The topcoat layer can be essentially free from any active agents or drugs.

In one embodiment, any or all of the layers of the stent coating, can be made of a polymer that is both biologically beneficial and biologically degradable, erodable, absorbable, and/or  
5 resorbable. In another embodiment, just the outermost layer of the coating can be limited to such a polymer.

To illustrate in more detail, in the stent coating having all three layers described above (i.e., the primer, the reservoir layer, and the topcoat layer), the outermost layer is the topcoat layer, which is made of a biologically absorbable block copolymer. In this case, optionally, the  
10 remaining layers (i.e., the primer and the reservoir layer) can be also fabricated of a biologically absorbable block copolymer ; the block copolymer can be the same or different in each layer. If the topcoat layer is not used, the stent coating can have only two layers: the optional primer and the reservoir. The reservoir in this case is the outermost layer of the stent coating and is made of a biologically absorbable block copolymer. Optionally, the primer can be also fabricated of a  
15 biologically absorbable block copolymer, which can be the same or different in the reservoir and in the primer. In one embodiment, the biologically absorbable copolymers that can be used for making any of the stent coating layers include poly(ester amides) (PEA). Optionally, in some other embodiments, condensation copolymers, such as poly(esters) having no amide bonds, can be used instead of PEAs.

20 The synthetic techniques that can be used for obtaining both the PEAs and the poly(esters) are described below in the application. Generally, the PEAs are products of reaction between at least one reagent from group A, at least one reagent from group B and a reagent C<sub>1</sub> from group C. The poly(esters) are products of reaction between at least one reagent from group

A and a reagent C<sub>2</sub> from group C. The precursor-reagents from groups A, B, and C that can be used are characterized as follows.

### A. Group A Reagents.

The group A precursor-reagents (hereinafter, "reagents") that can be used for synthesizing the biologically absorbable copolymers according to embodiments of the present invention are summarized in Table 1. The definition used to describe a chemical family to which each of the group A reagents belongs is also provided in Table 1.

Table 1. Group A Reagents

No.	Code	Reagent General Formula	Reagent Definition
1	A <sub>1</sub>	$\begin{array}{c} \text{R}_1 \quad \text{O} \quad \quad \quad \text{O} \quad \text{R}_1 \\   \quad    \quad \quad \quad    \quad   \\ \text{H}_2\text{N}-\text{CH}-\text{C}-\text{O}-\text{X}-\text{O}-\text{C}-\text{CH}-\text{NH}_2 \end{array}$	Diol-diamine
2	A <sub>2</sub>	$\begin{array}{c} \text{O} \quad \quad \quad \text{O} \\    \quad \quad \quad    \\ \text{HO}-\text{R}_2-\text{C}-\text{NH}-\text{Y}-\text{NH}-\text{C}-\text{R}_2-\text{OH} \end{array}$	Amidediol
3	A <sub>3</sub>	HO-X-OH	Diol
4	A <sub>4</sub>	H <sub>2</sub> N-Y-NH <sub>2</sub>	Diamine

In the general formulae of compounds A<sub>1</sub>, A<sub>2</sub>, A<sub>3</sub>, and A<sub>4</sub> presented in Table 1, the substituents R<sub>1</sub>, R<sub>2</sub>, X, and Y can be as follows:

R<sub>1</sub> – (a) hydrogen;

(b) methyl (–CH<sub>3</sub>);

(c) *iso*-propyl (–*i*-C<sub>3</sub>H<sub>7</sub>);

(d) *sec*-butyl (–*sec*-C<sub>4</sub>H<sub>9</sub>);

(e) *iso*-butyl (–*i*-C<sub>4</sub>H<sub>9</sub>); or

(f) benzyl (–C<sub>6</sub>H<sub>5</sub>);

R<sub>2</sub> – (a) methylene (–CH<sub>2</sub>–);

(b) ethylene (–CH<sub>2</sub>CH<sub>2</sub>–);

- (c) methylenemethylene [ $-\text{CH}(\text{CH}_3)-$ ];
- (d) straight chained or branched propylene, such as:
- (d1) *n*-propylene ( $-\text{CH}_2\text{CH}_2\text{CH}_2-$ );
- (d2) *iso*-propylene [ $-\text{CH}_2\text{CH}(\text{CH}_3)-$ ]; or
- 5 (d3) ethylenemethylene [ $-\text{CH}(\text{CH}_2\text{CH}_3)-$ ];
- (e) straight chained or branched butylene, such as:
- (e1) *n*-butylene ( $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ ),
- (e2) *iso*-butylene [ $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$ ], or
- (e3) *sec*-butylene [ $-\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2-$ ];
- 10 (f) straight chained or branched pentylene, such as:
- (f1) *n*-pentylene ( $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ ),
- (f2) *iso*-pentylene [ $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2-$ ],
- (f3) neopentylene [ $-\text{CH}[\text{C}(\text{CH}_3)_3]-$ ],
- (f4) 2-methyl-1-butylene [ $-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_3)\text{CH}_2-$ ],
- 15 (f5) *sec-iso*-pentylene [ $-\text{C}(\text{CH}_3)_2\text{CH}(\text{CH}_3)-$ ], or
- (f6) methylpropylenemethylene [ $-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CH}_3)-$ ]; or
- (g) groups that are present in some amino acids, such as:
- (g1) methyleneamide (present in asparagine) [ $-\text{CH}_2(\text{CONH}_2)-$ ];
- (g2) ethyleneamide (present in glutamine) [ $-\text{CH}_2\text{CH}_2(\text{CONH}_2)-$ ];
- 20 (g3) methylmercaptomethylenemethylene (present in methionine) [ $-\text{CH}_2(\text{CH}_2\text{SCH}_3)-$ ]; or
- (g4) *n*-propyleneamino group ( $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}-$ ) which is derived from 2-pyrrolidine group present (present in proline);

X – straight chained or branched aliphatic alkylene group  $\text{C}_n\text{H}_{2n}$ , wherein  $n$  is an integer between 2 and 16, e.g., methylene, ethylene, propylene, butylene, amylene (pentylene), hexylene, 25 heptylene, octylene, nonylene, decylene, undecylene, or dodecylene group; and

Y – straight chained or branched aliphatic alkylene group  $C_2H_4$  (ethylene),  $C_3H_6$  (propylene),  $C_4H_8$  (butylene), or  $C_5H_{10}$  (pentylene also known as amylene).

The reagent  $A_1$  is a diol-diamine that can be synthesized by condensation of two molar equivalents of an amino acid and one molar equivalent of a diol. The synthesis can be carried  
5 under the conditions favoring esterification of the amino acid via the amino acid's carboxyl group. The reaction can be conducted under dehydrating conditions which include anhydrous environment and an elevated temperature, for example, about  $50^\circ C$ , and can be catalyzed by a strong acid or base, e.g., *p*-toluenesulfonic acid.

The diol that can be used to make the reagent  $A_1$  has the formula  $HO-X-OH$ , where X is  
10 as defined above. Representative examples of diols that can be used include ethylene glycol, 1,3-propanediol, 1,4-butane diol, 1,5-pentanediol, 1,6-hexanediol, 1,7-heptanediol, 1,8-octanediol, 1,9-nonanediol, 1,10-decanediol, 1,11-undecanediol, and 1,12-dodecanediol. The amino acid that can be used to make the reagent  $A_1$  has the formula  $H_2N-CHR_1-COOH$ , where  $R_1$  is as defined above. Some amino acids that can be used are summarized in Table 2.

Table 2. Amino Acids That Can Be Used for Making the Reagent A<sub>1</sub>

No.	R <sub>1</sub>	Amino Acid (H <sub>2</sub> N—CHR <sub>1</sub> —COOH)	
		Formula	Name
1	—H	H <sub>2</sub> N—CH <sub>2</sub> —COOH	glycine
2	—CH <sub>3</sub>	$\begin{array}{c} \text{CH}_3 \\   \\ \text{H}_2\text{N}-\text{CH}-\text{COOH} \end{array}$	alanine
3	— <i>i</i> -C <sub>3</sub> H <sub>7</sub>	$\begin{array}{c} \text{CH}_3-\text{CH}-\text{CH}_3 \\   \\ \text{H}_2\text{N}-\text{CH}-\text{COOH} \end{array}$	valine
4	— <i>sec</i> -C <sub>4</sub> H <sub>9</sub>	$\begin{array}{c} \text{CH}_3-\text{CH}_2-\text{CH}-\text{CH}_3 \\   \\ \text{H}_2\text{N}-\text{CH}-\text{COOH} \end{array}$	isoleucine
5	— <i>i</i> -C <sub>4</sub> H <sub>9</sub>	$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3-\text{CH}-\text{CH}_2 \\   \\ \text{H}_2\text{N}-\text{CH}-\text{COOH} \end{array}$	leucine
6	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> —	$\begin{array}{c} \text{C}_6\text{H}_5-\text{CH}_2 \\   \\ \text{H}_2\text{N}-\text{CH}-\text{COOH} \end{array}$	phenyl alanine
7	—(CH <sub>2</sub> ) <sub>2</sub> —S—CH <sub>3</sub>	$\begin{array}{c} \text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_3 \\   \\ \text{H}_2\text{N}-\text{CH}-\text{COOH} \end{array}$	methionine (α-amino-γ-methylmercaptobutyric acid)
8	—CH <sub>2</sub> —C(O)—NH <sub>2</sub>	$\begin{array}{c} \text{CH}_2-\text{C(O)}-\text{NH}_2 \\   \\ \text{H}_2\text{N}-\text{CH}-\text{COOH} \end{array}$	asparagine (α-amino-succinamic acid)
9	—(CH <sub>2</sub> ) <sub>2</sub> —C(O)—NH <sub>2</sub>	$\begin{array}{c} \text{CH}_2-\text{CH}_2-\text{C(O)}-\text{NH}_2 \\   \\ \text{H}_2\text{N}-\text{CH}-\text{COOH} \end{array}$	glutamine (2-amino-glutaramic acid)

In addition to amino acids listed in Table 2, alternatively other amino acids can be used.

One example of such alternative amino acids is proline (2-pyrrolidine carboxylic acid). Other

alternative amino acids that can be used include some amino acids having free hydroxyl groups

5 or second carboxyl groups if the free hydroxyl groups or the second carboxyl groups are

protected first. The protection is needed so as to avoid interference when reagent A<sub>1</sub> is

subsequently reacted with reagents of groups B and C, as discussed above. Examples of the



amino acids that can be used after the free hydroxyl or second carboxyl groups are protected include tyrosine, serine, or glutamic acid.

The reagent  $A_2$  is an amidediol that can be synthesized by condensation of two molar equivalents of a hydroxy acid and one molar equivalent of a diamine. The synthesis can be  
5 carried under the conditions favoring formation of an amide bond. The reaction can be conducted under dehydrating conditions, which include anhydrous environment and can be catalyzed by a strong base. Simple heating of the neat starting materials with the simultaneous removal of generated water by distillation can also be used.

The diamine that can be used to make the reagent  $A_2$  has the formula  $H_2N-Y-NH_2$ ,  
10 where Y is as defined above. Accordingly, examples of diamines that can be used include 1,4-butanedi-amine (putrescine) ( $Y = CH_2CH_2CH_2CH_2$ ). Alternatively, other diamines, such as 1,2-ethanedi-amine ( $Y = CH_2CH_2$ ) or 1,5-pentanedi-amine (cadavarene) ( $Y = CH_2CH_2CH_2CH_2CH_2$ ) can be used. The hydroxy acid that can be used to make the reagent  $A_2$  has the formula  $HO-R_2-COOH$ , where  $R_2$  is as defined above. Some hydroxy acids that can be used are  
15 summarized in Table 3.

Table 3. Hydroxy Acids That Can Be Used For Making The Reagent A<sub>2</sub>

No.	R <sub>2</sub>	Hydroxy Acid (HO—R <sub>2</sub> —COOH)	
		Formula	Name
1	—CH <sub>2</sub> —	HO—CH <sub>2</sub> —COOH	glycolic (hydroxyacetic) acid
2	—CH <sub>2</sub> —CH <sub>2</sub> —	HO—CH <sub>2</sub> —CH <sub>2</sub> —COOH	β-hydroxypropionic acid
3	$\begin{array}{c} \text{—CH—} \\   \\ \text{CH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3 \\   \\ \text{HO—CH—COOH} \end{array}$	lactic (α-hydroxypropionic) acid
4	$\begin{array}{c} \text{—CH—CH}_2\text{—} \\   \\ \text{CH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3 \\   \\ \text{HO—CH—CH}_2\text{—COOH} \end{array}$	β-hydroxybutyric acid
5	$\begin{array}{c} \text{—CH—} \\   \\ \text{CH}_2\text{—CH}_2\text{—CH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3\text{—CH}_2\text{—CH}_2 \\   \\ \text{HO—CH—COOH} \end{array}$	α-hydroxyvaleric acid
6	$\begin{array}{c} \text{—CH—CH}_2\text{—} \\   \\ \text{CH}_2\text{—CH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3\text{—CH}_2 \\   \\ \text{HO—CH—CH}_2\text{—COOH} \end{array}$	β-hydroxyvaleric acid
7	—(CH <sub>2</sub> ) <sub>5</sub> —	HO—(CH <sub>2</sub> ) <sub>5</sub> —COOH	ε-hydroxycaproic acid
8	$\begin{array}{c} \text{—CH—} \\   \\ \text{CH}_3\text{—(CH}_2\text{)}_2\text{—CH}_2 \end{array}$	$\begin{array}{c} \text{CH}_3\text{—(CH}_2\text{)}_3\text{—CH—COOH} \\   \\ \text{OH} \end{array}$	α -hydroxycaproic acid
8	$\begin{array}{c} \text{—CH—CH}_2\text{—} \\   \\ \text{CH}_3\text{—CH}_2\text{—CH}_2 \end{array}$	$\begin{array}{c} \text{CH}_3\text{—(CH}_2\text{)}_2\text{—CH—CH}_2\text{—COOH} \\   \\ \text{OH} \end{array}$	β-hydroxycaproic acid
9	$\begin{array}{c} \text{—(CH}_2\text{)}_2\text{—CH—} \\   \\ \text{CH}_3\text{—CH}_2 \end{array}$	$\begin{array}{c} \text{CH}_3\text{—CH}_2\text{—CH—(CH}_2\text{)}_2\text{—COOH} \\   \\ \text{OH} \end{array}$	δ-hydroxycaproic acid

The reagent A<sub>3</sub> is a common simple diol having the formula HO—X—OH, where X is as defined above; and the reagent A<sub>4</sub> is a common simple diamine having the formula

- 5 H<sub>2</sub>N—Y—NH<sub>2</sub>, where Y is as defined above.

**B. Group B Reagents.**

The group B reagents that can be used for synthesizing the biologically absorbable copolymers according to embodiments of the present invention are summarized in Table 4.

Exemplary definitions used to describe a chemical family to which each of the group B reagents

5 belongs is also provided in Table 4.

Table 4. Group B Reagents

No.	Code	Reagent General Formula	Exemplary Reagent Definition ( $R_4 = \text{PEG}$ )
1	B <sub>1</sub>	$\begin{array}{c} R_1 \quad O \quad O \quad R_1 \\   \quad    \quad    \quad   \\ H_2N-CH-C-O-R_4-O-C-CH-NH_2 \end{array}$	PEG-diester-diamine
2	B <sub>2</sub>	$\begin{array}{c} O \quad O \\    \quad    \\ HO-R_2-C-NH-R_4-NH-C-R_2-OH \end{array}$	PEG-amidediol
3	B <sub>3</sub>	HO-R <sub>4</sub> -OH	PEG-diol
4	B <sub>4</sub>	H <sub>2</sub> N-R <sub>4</sub> -NH <sub>2</sub>	PEG-diamine

In general formulae of compounds B<sub>1</sub>, B<sub>2</sub>, B<sub>3</sub>, and B<sub>4</sub> presented in Table 4, the substituents R<sub>1</sub> and R<sub>2</sub> are as defined above. One example of the R<sub>4</sub> moiety that can be used is a moiety derived from poly(ethylene glycol) (PEG). Alternatively, other biologically beneficial moieties can be used as R<sub>4</sub>, for example, moieties derived from poly(propylene glycol) (PPG), random or block copolymers of PEG and PPG, hyaluronic acid, poly(2-hydroxyethylmethacrylate), poly(3-hydroxypropylmethacrylamide), or celluloses.

The reagent B<sub>1</sub> can be a PEG-diester-diamine moiety (i.e., when R<sub>4</sub> = PEG) that can be synthesized by condensation of two molar equivalents of an amino acid and one molar equivalent of PEG. The synthesis can be carried under the conditions favoring esterification of the amino acid via the carboxyl group. The reaction can be conducted under dehydrating conditions which include anhydrous environment and an elevated temperature, for example, about 50°C, and can be catalyzed by a strong acid or base, e.g., *p*-toluenesulfonic acid. To make the reagent B<sub>1</sub>, PEG

having molecular weight between about 100 and 4,000 Daltons, for example, about 300 Daltons, can be used. Any amino acid listed in Table 2 can be used. Alternatively, other amino acids can be used, for example, tyrosine, serine, or glutamic acid, if free hydroxyl groups of tyrosine and serine or the second carboxyl group of glutamic acid are protected so as not to interfere when  
5 reagent B<sub>1</sub> is subsequently reacted with reagents of groups A and C, as discussed above.

The reagent B<sub>2</sub> can be a PEG-amidediol that can be synthesized by condensation of two molar equivalents of a hydroxy acid and one molar equivalent of a PEG-diamine. The synthesis can be carried under the conditions favoring formation of an amide bond. The reaction can be conducted under dehydrating conditions which include anhydrous environment, and can be  
10 catalyzed by a strong base, or prepared from neat reagents by heating at high temperature with the simultaneous removal of generated water, e.g., the removal of water by distillation. Any hydroxy acid listed in Table 3 can be used. PEG terminated with amino groups on both ends (PEG-diamine reagent B<sub>4</sub>) can be obtained from Huntsman Chemical Co. of Houston, Texas under the trade name JEFFAMINE.

15 **C. Group C Reagents.**

The group C reagents that can be used for synthesizing the biologically absorbable copolymers according to embodiments of the present invention are summarized in Table 5. The definition used to describe a chemical family to which each of the group C reagents belongs is also provided in Table 5.

Table 5. Group C Reagents

No.	Code	Reagent General Formula	Reagent Definition
1	C <sub>1</sub>	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-\text{R}_3-\text{C}-\text{OH} \end{array}$	Dicarboxylic acid
2	C <sub>2</sub>	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HO}-\text{C}-\text{PEG}-\text{C}-\text{OH} \end{array}$	PEG-dicarboxylic acid

In general formula of compound C<sub>1</sub> presented in Table 5, the substituent R<sub>3</sub> is simply a covalent bond, or a straight chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is an integer having a value between 0 and 12, e.g. a single bond (n = 0), methylene, ethylene, propylene, butylene, amylene (pentylene), hexylene, heptylene, octylene, nonylene, decylene, undecylene, or dodecylene group, or an aromatic group, e.g., phenyl or *para*-phenylene. Some examples of dicarboxylic acids that can be used as the reagent C<sub>1</sub> are summarized in Table 6.

Table 6. Dicarboxylic Acids That Can Be Used As The Reagent C<sub>1</sub>

No.	R <sub>3</sub>	Dicarboxylic Acid (HOOC—R <sub>3</sub> —COOH)	
		Formula	Name
1	—(CH <sub>2</sub> ) <sub>2</sub> —	HOOC—(CH <sub>2</sub> ) <sub>2</sub> —COOH	succinic (butanedioic) acid
2	—(CH <sub>2</sub> ) <sub>4</sub> —	HOOC—(CH <sub>2</sub> ) <sub>4</sub> —COOH	adipic (hexanedioic) acid
3	—(CH <sub>2</sub> ) <sub>8</sub> —	HOOC—(CH <sub>2</sub> ) <sub>8</sub> —COOH	sebacic (decanedioic) acid
4	( <i>p</i> )—C <sub>6</sub> H <sub>4</sub> —	HOOC—( <i>p</i> )C <sub>6</sub> H <sub>4</sub> —COOH	terephthalic (1,4-benzene dicarboxylic) acid

In addition to the dicarboxylic acids listed in Table 6, examples of other dicarboxylic acids that can be also used include oxalic acid, malonic acid, glutaric acid, pimelic acid, suberic acid, or azelaic acid. As mentioned above, to synthesize the PEAs, at least one reagent of group A can be reacted with at least one reagent of group B and reagent C<sub>1</sub>. To make the poly(esters), at least one reagent of group A can be reacted with reagent C<sub>2</sub>.

One of several routes can be utilized to synthesize the polymers of this invention. Those having ordinary skill in the art can appreciate that the reagents of groups A, B, and C may themselves contain hydrolysable bonds, i.e. ester or amide bonds. These reagents can be then polymerized, the polymerization creating additional bonds that may be both ester and amide bonds, only amide bonds, or only ester bonds. Given that the reagents can be obtained separately, the types of polymers formed during the polymerization can belong to one of the following four categories (A), (B), (C), or (D):

(A) Polymers in which amide bonds are formed between reagents which themselves contain ester bonds. Using the reagent codes defined earlier, these polymers can be described as products of reaction between:

(1)  $A_1$ ,  $B_1$  and  $C_1$  ( $A_1$ - $B_1$ - $C_1$ );

(2)  $A_1$ ,  $B_4$  and  $C_1$  ( $A_1$ - $B_4$ - $C_1$ );

(3)  $A_4$ ,  $B_1$  and  $C_1$  ( $A_4$ - $B_1$ - $C_1$ ); and

(4)  $A_1$  and  $C_2$  ( $A_1$ - $C_2$ ).

(B) Polymers in which amide bonds are formed between reagents which themselves contain neither ester nor amide bonds. Using the reagent codes defined earlier, these polymers can be described as products of reaction between:

(1)  $A_4$ ,  $B_4$  and  $C_1$  ( $A_4$ - $B_4$ - $C_1$ ); and

(2)  $A_4$  and  $C_2$  ( $A_4$ - $C_2$ ).

(C) Polymers in which both ester and amide bonds are formed between the reagents. The subunits themselves may contain ester and amide bonds, only ester bonds, only amide bonds,

or neither ester nor amide bonds. Using the reagent codes defined earlier, these polymers can be described as products of reaction between:

- (1) A<sub>1</sub>, B<sub>2</sub> and C<sub>1</sub> (A<sub>1</sub>-B<sub>2</sub>-C<sub>1</sub>);
- (2) A<sub>1</sub>, B<sub>3</sub> and C<sub>1</sub> (A<sub>1</sub>-B<sub>3</sub>-C<sub>1</sub>);
- 5 (3) A<sub>2</sub>, B<sub>1</sub> and C<sub>1</sub> (A<sub>2</sub>-B<sub>1</sub>-C<sub>1</sub>);
- (4) A<sub>2</sub>, B<sub>4</sub> and C<sub>1</sub> (A<sub>2</sub>-B<sub>4</sub>-C<sub>1</sub>);
- (5) A<sub>3</sub>, B<sub>1</sub> and C<sub>1</sub> (A<sub>3</sub>-B<sub>1</sub>-C<sub>1</sub>);
- (6) A<sub>3</sub>, B<sub>4</sub> and C<sub>1</sub> (A<sub>3</sub>-B<sub>4</sub>-C<sub>1</sub>);
- (7) A<sub>4</sub>, B<sub>2</sub> and C<sub>1</sub> (A<sub>4</sub>-B<sub>2</sub>-C<sub>1</sub>); and
- 10 (8) A<sub>4</sub>, B<sub>3</sub> and C<sub>1</sub> (A<sub>4</sub>-B<sub>3</sub>-C<sub>1</sub>).

(D) Polymers in which ester bonds are formed between reagents which themselves may contain amide bonds, or neither amide nor ester bonds. Using the reagent codes defined earlier, these polymers can be described as products of reaction between:

- (1) A<sub>2</sub>, B<sub>2</sub> and C<sub>1</sub> (A<sub>2</sub>-B<sub>2</sub>-C<sub>1</sub>);
- 15 (2) A<sub>2</sub>, B<sub>3</sub> and C<sub>1</sub> (A<sub>2</sub>-B<sub>3</sub>-C<sub>1</sub>);
- (3) A<sub>2</sub> and C<sub>2</sub> (A<sub>2</sub>-C<sub>2</sub>);
- (4) A<sub>3</sub>, B<sub>2</sub> and C<sub>1</sub> (A<sub>3</sub>-B<sub>2</sub>-C<sub>1</sub>);
- (5) A<sub>3</sub>, B<sub>3</sub> and C<sub>1</sub> (A<sub>3</sub>-B<sub>3</sub>-C<sub>1</sub>); and

(6) A<sub>3</sub> and C<sub>2</sub> (A<sub>3</sub>-C<sub>2</sub>).

Due to the types of bonds being formed, and the types of bonds present, those having ordinary skill in the art will understand that the polymerization scheme need be adjusted for each category in order to form the desired polymer while not hydrolyzing or degrading the existing  
 5 bonds in the reagents, or creating uncontrolled, mixed species. Some examples of the synthesis of particular polymers are provided below in the "Examples" section of the present application.

As a result of the synthesis, biologically absorbable PEAs having a general formula (A) or poly(esters) having a general formula (B) can be obtained:

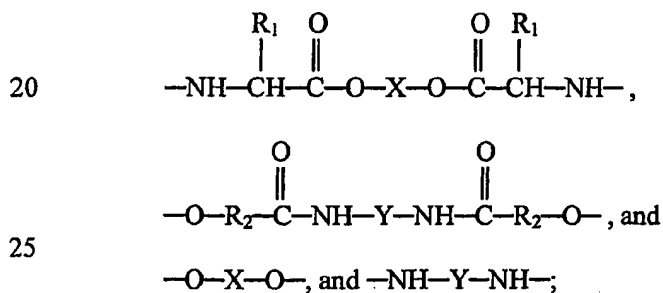


wherein:

M is a moiety represented by the structure

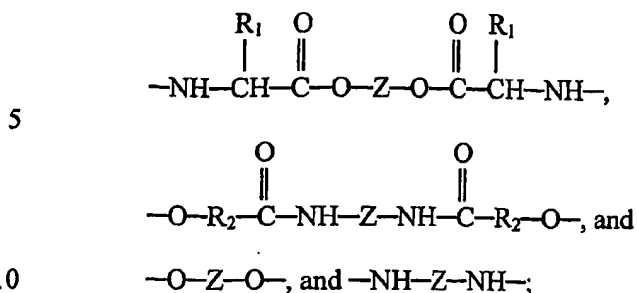


P is a moiety including





Q is a moiety selected from a group consisting of



M<sub>1</sub> is a moiety represented by the structure



R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, X and Y are substituents and moieties as defined above;

Z is a moiety that can be derived from a compound selected from a group consisting of poly(ethylene glycol)(PEG), poly(propylene glycol) (PPG), random or block copolymers of PEG  
20 and PPG, hyaluronic acid, poly(2-hydroxyethylmethacrylate), poly(3-hydroxypropyl methacrylamide), poly(styrene sulfonate), poly(vinyl pyrrolidone, and cellulose; and

m, n, and p are integers where the value of m can be between 5 and 1,800, the value of n can be between 1 and 800 and the value of p can be between 4 and 1,500.

Any layer of the stent coating can contain any amount of the biologically absorbable  
25 copolymers described above, or a blend of more than one of such copolymers. If less than 100% of the layer is made of the biologically absorbable copolymers, or blends thereof, described above, alternative polymers can comprise the balance. Examples of the alternative polymers that can be used include polyacrylates, such as poly(butyl methacrylate), poly(ethyl methacrylate), and poly(ethyl methacrylate-co-butyl methacrylate), and fluorinated polymers and/or copolymers,

such as poly(vinylidene fluoride) and poly(vinylidene fluoride-co-hexafluoropropene), poly(N-vinyl pyrrolidone), poly(hydroxyvalerate), poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), co-poly(ether-esters), polyalkylene oxalates, polyphosphazenes, biomolecules (such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid), polyurethanes, silicones, polyesters, polyolefins, polyisobutylene and ethylene-alphaolefin copolymers, vinyl halide polymers and copolymers (such as polyvinyl chloride), polyvinyl ethers (such as polyvinyl methyl ether), polyvinylidene chloride, polyacrylonitrile, polyvinyl ketones, polyvinyl aromatics (such as polystyrene), polyvinyl esters (such as polyvinyl acetate), copolymers of vinyl monomers with each other and olefins, e.g., poly(ethylene-co-vinyl alcohol) (EVAL), ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides (such as Nylon 66 and polycaprolactam), alkyd resins, polycarbonates, polyoxymethylenes, polyimides, polyethers, epoxy resins, polyurethanes, rayon, rayon-triacetate, cellulose, cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, and carboxymethyl cellulose.

Representative examples of some solvents suitable for making the stent coatings include N,N-dimethylacetamide (DMAC), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), cyclohexanone, xylene, toluene, acetone, *i*-propanol, methyl ethyl ketone, propylene glycol monomethyl ether, methyl butyl ketone, ethyl acetate, *n*-butyl acetate, and dioxane. Some solvent mixtures can be used as well. Representative examples of the mixtures include:

(1) DMAC and methanol (e.g., a 50:50 by mass mixture);

- (2) water, *i*-propanol, and DMAC (e.g., a 10:3:87 by mass mixture);
- (3) *i*-propanol, and DMAC (e.g., 80:20, 50:50, or 20:80 by mass mixtures);
- (4) acetone and cyclohexanone (e.g., 80:20, 50:50, or 20:80 by mass mixtures);
- (5) acetone and xylene (e.g. a 50:50 by mass mixture);
- 5 (6) acetone, FLUX REMOVER AMS, and xylene (e.g., a 10:50:40 by mass mixture); and
- (7) 1,1,2-trichloroethane and chloroform (e.g., a 80:20 by mass mixture).

FLUX REMOVER AMS is trade name of a solvent manufactured by Tech Spray, Inc. of Amarillo, Texas comprising about 93.7% of a mixture of 3,3-dichloro-1,1,1,2,2-pentafluoropropane and 1,3-dichloro-1,1,2,2,3-pentafluoropropane, and the balance of methanol,  
10 with trace amounts of nitromethane. Those having ordinary skill in the art will select the solvent or a mixture of solvents suitable for a particular polymer being dissolved.

The therapeutic substance which can be used in the reservoir layer can include any substance capable of exerting a therapeutic or prophylactic effect for a patient. The therapeutic substance may include small molecule substances, peptides, proteins, oligonucleotides, and the  
15 like. The therapeutic substance could be designed, for example, to inhibit the activity of vascular smooth muscle cells. It can be directed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells to inhibit restenosis.

Examples of therapeutic substances that can be used include antiproliferative substances such as actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich of  
20 Milwaukee, Wisconsin, or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I<sub>1</sub>, actinomycin X<sub>1</sub>, and actinomycin C<sub>1</sub>.

The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g. TAXOL<sup>®</sup> by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g. Taxotere<sup>®</sup>, from  
5 Aventis S.A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin<sup>®</sup> from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin<sup>®</sup> from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost,  
10 prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as ANGIOMAX (Biogen, Inc., Cambridge, Mass.). Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten<sup>®</sup> and Capozide<sup>®</sup> from  
15 Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil<sup>®</sup> and Prinzide<sup>®</sup> from Merck & Co., Inc., Whitehouse Station, NJ); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor<sup>®</sup> from Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such  
20 as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, tacrolimus,  
25 dexamethasone, and rapamycin and structural derivatives or functional analogs thereof, such as

40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of EVEROLIMUS available from Novartis), 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-O-tetrazole-rapamycin.

The coatings and methods of the present invention have been described with reference to a  
5 stent, e.g., a balloon expandable or self-expandable stent. The use of the coating is not limited to  
stents, and the coating can also be used with a variety of other medical devices, such as implantable  
medical devices. Examples of the implantable medical device that can be used in conjunction with  
the embodiments of this invention include stent-grafts, grafts (e.g., aortic grafts), catheters,  
guidewires, artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, axis coronary  
10 shunts and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corporation  
The underlying structure of the device can be of virtually any design. The device can be made of a  
metallic material or an alloy such as, but not limited to, cobalt-chromium alloys (e.g., ELGILOY),  
stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, tantalum-based  
alloys, nickel-titanium alloy, platinum, platinum-based alloys such as, e.g., platinum-iridium alloy,  
15 iridium, gold, magnesium, titanium, titanium-based alloys, zirconium-based alloys, or combinations  
thereof. Devices made from bioabsorbable or biostable polymers can also be used with the  
embodiments of the present invention. "MP35N" and "MP20N" are trade names for alloys of cobalt  
nickel, chromium and molybdenum available from Standard Press Steel Co. of Jenkintown,  
Pennsylvania. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum  
20 "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum.

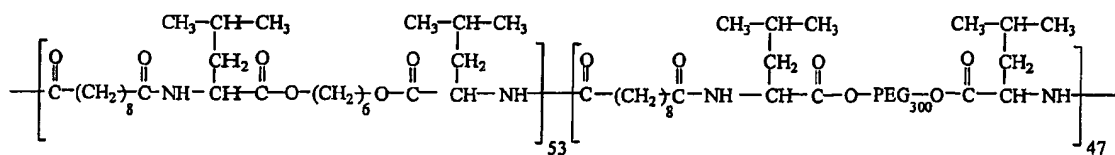
Medical devices can be also made from the materials of the invention. Moreover, the  
polymers can be used for a variety of medical applications, including particles for drug delivery to  
embolize blood vessels. The polymers of the present invention can have a variety of medical  
applications, including the treatment of stenosis, restenosis, and cancer.

### 3. Examples.

The following examples are provided to further illustrate embodiments of the present invention.

#### Example 1

5 A copolymer having formula (III) can be synthesized and used in practice of the invention.



(III)

10 The copolymer (III) is a product of copolymerization of reagents A<sub>1</sub>, B<sub>1</sub>, and C<sub>1</sub>. A<sub>1</sub> can be a diol-diamine shown in Table 1 where R<sub>1</sub> is *i*-C<sub>4</sub>H<sub>9</sub> and X is (CH<sub>2</sub>)<sub>6</sub>. In other words, A<sub>1</sub> can be synthesized by condensation of leucine with 1,6-hexanediol. B<sub>1</sub> can be a PEG-diester-diamine shown in Table 4 where R<sub>1</sub> is *i*-C<sub>4</sub>H<sub>9</sub> and PEG<sub>300</sub> symbolizes a moiety derived from poly(ethylene glycol) having molecular weight of about 300 Daltons. In other words, B<sub>1</sub> can be synthesized by condensation of leucine with poly(ethylene glycol) having molecular weight of about 300 Daltons. C<sub>1</sub> can be a dicarboxylic acid shown in Table 5 where R<sub>3</sub> is (CH<sub>2</sub>)<sub>8</sub> (sebacic acid, which is also shown in Table 6).

To synthesize copolymer (III), about 30.8 ml dry triethylamine (about 0.22 mole) in about 55 ml dry solvent N,N'-dimethylacetamide at room temperature can be added to a mixture of:

(a) about 36.37 g (about 0.053 mole) di-*para*-toluenesulfonic acid salt of *bis*-(L-leucine)-1,6-hexylene diester;

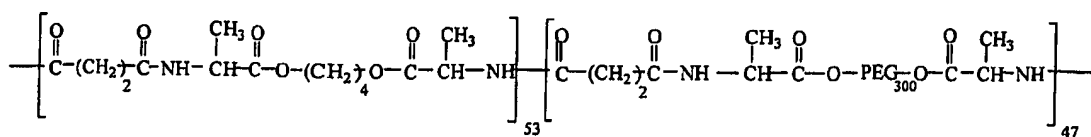
(b) about 39.3 g (about 0.047 mole) di-*para*-toluenesulphonic acid salt of *bis*-(L-leucine)-PEG300 diester; and

5 (c) about 44.4 g (about 0.1 mole) di-*para*-nitrophenyl sebacinate.

The mixture can be stirred until full dissolution and then the temperature can be raised to about 80°C. After stirring for about 24 hours, the viscous mixture can be cooled to room temperature, diluted with about 100 ml ethanol, and precipitated into an excess of water. The separated polymer can be thoroughly washed with water, spread thinly onto a TEFLON pan, and  
 10 dried at room temperature under vacuum (about 70 mm Hg) for about 24 hours.

### Example 2

A copolymer having formula (IV) can be synthesized and used in practice of the invention.



15

(IV)

The copolymer (IV) is a product of copolymerization of reagents A<sub>1</sub>, B<sub>1</sub>, and C<sub>1</sub>. A<sub>1</sub> can be a diol-diamine shown in Table 1, where R<sub>1</sub> is CH<sub>3</sub> and X is (CH<sub>2</sub>)<sub>4</sub>. In other words, A<sub>1</sub> can be synthesized by condensation of alanine with 1,4-butanediol. B<sub>1</sub> can be a PEG-diester-diamine

shown in Table 4 where  $R_1$  is  $i\text{-C}_4\text{H}_9$  and  $\text{PEG}_{300}$  symbolizes a moiety derived from poly(ethylene glycol) having molecular weight of about 300 Daltons. In other words,  $B_1$  can be synthesized by condensation of alanine with poly(ethylene glycol) having molecular weight of about 300 Daltons.  $C_1$  can be a dicarboxylic acid shown in Table 5 where  $R_3$  is  $(\text{CH}_2)_2$  (succinic acid, which is also shown in Table 6).

To synthesize copolymer (IV), about 30.8 ml dry triethylamine (about 0.22 mole), in about 55 ml dry solvent  $N,N'$ -dimethylacetamide, at room temperature, can be added to a mixture of:

(a) about 30.43 g (about 0.053 mole) di-*para*-toluenesulfonic acid salt of *bis*-(L-alanine)-1,4-butylene diester;

(b) about 36.86 g (about 0.047 mole) di-*para*-toluenesulfonic acid salt of *bis*-(L-alanine)-PEG300 diester; and

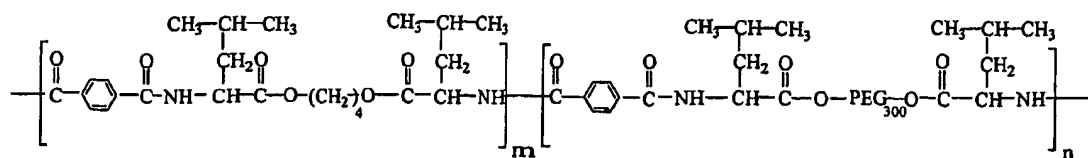
(c) about 36.0 g (about 0.1 mole) di-*para*-nitrophenyl succinate.

The mixture can be stirred until full dissolution and then the temperature can be raised to about 80°C. After stirring for about 24 hours, the viscous mixture can be cooled to room temperature, diluted with about 100 ml ethanol, and precipitated into an excess of water. The separated polymer is thoroughly washed with water, spread thinly into a TEFLON pan, and dried at room temperature under vacuum (about 70 mm Hg) for about 24 hours.

### Example 3

A copolymer having formula (V) can be synthesized and used in practice of the invention.





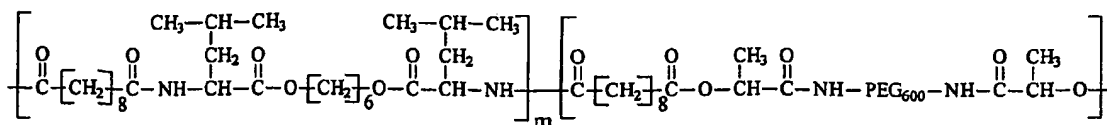
(V)

The copolymer (V) is a product of copolymerization of reagents A<sub>1</sub>, B<sub>1</sub>, and C<sub>1</sub>. A<sub>1</sub> can be a diol-diamine shown in Table 1 where R<sub>1</sub> is *i*-C<sub>4</sub>H<sub>9</sub> and X is (CH<sub>2</sub>)<sub>4</sub>. In other words, A<sub>1</sub> can be synthesized by condensation of leucine with 1,4-butanediol. B<sub>1</sub> can be a PEG-diester-diamine shown in Table 4 where R<sub>1</sub> is *i*-C<sub>4</sub>H<sub>9</sub> and PEG<sub>300</sub> symbolizes a moiety derived from poly(ethylene glycol) having molecular weight of about 300 Daltons. In other words, B<sub>1</sub> can be synthesized by condensation of leucine with poly(ethylene glycol) having molecular weight of about 300 Daltons. C<sub>1</sub> can be a dicarboxylic acid shown in Table 5 where R<sub>3</sub> is *para*-C<sub>6</sub>H<sub>4</sub> (terephthalic acid, which is also shown in Table 6).

The copolymer (V) can be obtained using the same synthetic technique as described in Example 2 for copolymer (IV), except di-*para*-nitrophenyl terephthalate can be used to make the copolymer (V), instead of di-*para*-nitrophenyl succinate. In copolymer (V), the value of n can be between about 64 and about 97 and the value of m can be between about 3 and about 36, where m + n = 100.

#### Example 4

A copolymer having formula (VI) can be synthesized and used in practice of the invention.



(VI)

The copolymer (VI) is a product of copolymerization of reagents A<sub>1</sub>, B<sub>2</sub>, and C<sub>1</sub>. A<sub>1</sub> can be a diol-diamine shown in Table 1 where R<sub>1</sub> is *i*-C<sub>4</sub>H<sub>9</sub> and X is (CH<sub>2</sub>)<sub>6</sub>. In other words, A<sub>1</sub> can be synthesized by condensation of leucine with 1,6-hexanediol. B<sub>2</sub> can be a PEG-amidediol shown in Table 4 where R<sub>2</sub> is methylenemethylene CH(CH<sub>3</sub>).

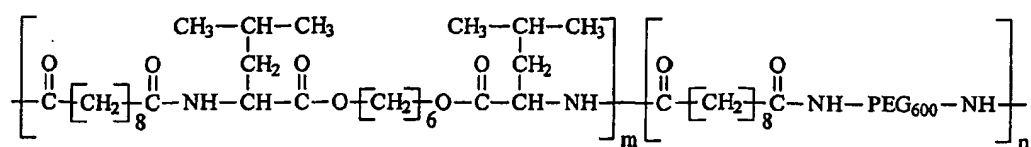
In other words, B<sub>2</sub> can be synthesized by condensation of lactic acid with PEG-diamine shown as reagent B<sub>4</sub> in Table 4. PEG-diamine can be based on poly(ethylene glycol) having molecular weight of about 600 Daltons, which is symbolized by the abbreviation PEG<sub>600</sub>.

For example, JEFFAMINE ED-600 available from Huntsman Corp. can be used. JEFFAMINE ED-600 is a trade name of O,O'-bis-[(2-aminopropyl) poly(propylene glycol)-block-poly(ethylene glycol)-block-poly(propylene glycol)], which is a polyether diamine with a polyalkylene oxide backbone. The molecular weight of JEFFAMINE ED-600 is about 600 Daltons.

C<sub>1</sub> can be a dicarboxylic acid shown in Table 5 where R<sub>3</sub> is (CH<sub>2</sub>)<sub>8</sub> (sebacic acid, which is also shown in Table 6). In copolymer (VI), the value of n can be between about 60 and about 93 and the value of m can be between about 7 and about 40, where m + n = 100.

#### Example 5

A copolymer having formula (VII) can be synthesized and used in practice of the invention.

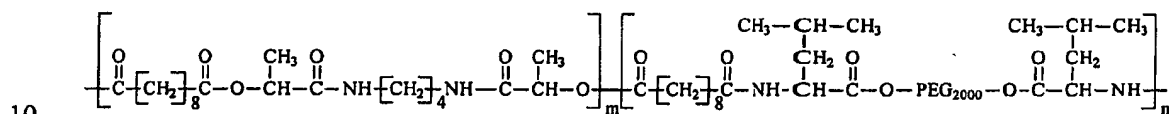


(VII)

The copolymer (VII) can be synthesized in same way as the copolymer (VI) of Example 4, except instead of a reagent B<sub>2</sub> (e.g., PEG-amidediol), reagent B<sub>4</sub> (e.g., PEG-diamine) shown in Table 4 can be used. In copolymer (VII), the value of n can be between about 59 and about 96 and the value of m can be between about 4 and about 41, where  $m + n = 100$ .

#### Example 6

A copolymer having formula (VIII) can be synthesized and used in practice of the invention.



(VIII)

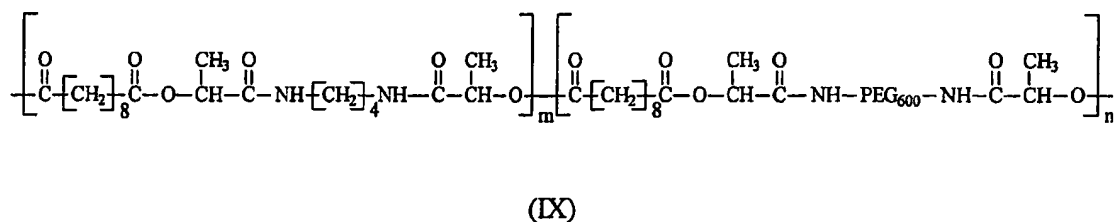
The copolymer (VIII) is a product of copolymerization of reagents A<sub>2</sub>, B<sub>1</sub>, and C<sub>1</sub>. A<sub>2</sub> can be an amidediol shown in Table 1 where R<sub>2</sub> is methylmethylene CH(CH<sub>3</sub>) and Y is (CH<sub>2</sub>)<sub>4</sub>. In other words, A<sub>2</sub> can be synthesized by condensation of lactic acid with the 1,4-diamino butane (putrescine).

B<sub>1</sub> can be a PEG-diester-diamine shown in Table 4 where R<sub>1</sub> is *i*-C<sub>4</sub>H<sub>9</sub>. In other words, B<sub>1</sub> can be synthesized by condensation of leucine with poly(ethylene glycol) having molecular weight of about 2,000 Daltons, which is symbolized by the abbreviation PEG<sub>2000</sub>.

C<sub>1</sub> can be a dicarboxylic acid shown in Table 5 where R<sub>3</sub> is (CH<sub>2</sub>)<sub>8</sub> (sebacic acid, which is also shown in Table 6). In copolymer (VIII), the value of n can be between about 86 and about 99 and the value of m can be between about 1 and about 14, where m + n = 100.

#### Example 7

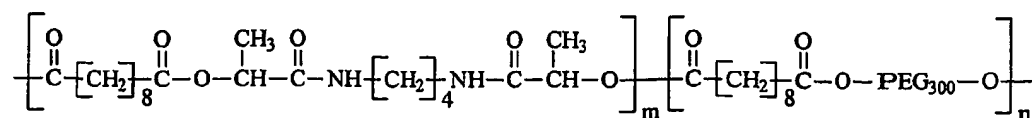
- 5 A copolymer having formula (IX) can be synthesized and used in practice of the invention.



- The copolymer (IX) can be synthesized in same way as the copolymer (VIII) of Example 6, except instead of a reagent B<sub>1</sub> (PEG-diester-diamine), reagent B<sub>2</sub> (PEG-amidediol) shown in Table 4 can be used, where R<sub>2</sub> is methylnethylene CH(CH<sub>3</sub>). In other words, B<sub>2</sub> can be synthesized by condensation of lactic acid with PEG-diamine shown as reagent B<sub>4</sub> in Table 4. PEG-diamine can be based on poly(ethylene glycol) having molecular weight of about 600 Daltons, which is symbolized by the abbreviation PEG<sub>600</sub>. In copolymer (IX), the integer value of n can be between about 69 and about 98 and the value of m can be between about 2 and about 31, where m + n = 100.

#### Example 8

A copolymer having formula (X) can be synthesized and used in practice of the invention.



(X)

The copolymer (X) can be synthesized in same way as the copolymer (IX) of Example 7, except that a reagent B<sub>3</sub> shown in Table 4, (HO-R<sub>4</sub>-OH), for example, PEG-diol, can be used  
 5 instead of a reagent B<sub>2</sub> (e.g., PEG-amidediol). PEG-diol can be based on poly(ethylene glycol) having molecular weight of about 300 Daltons, which is symbolized by the abbreviation PEG<sub>300</sub>.

A<sub>2</sub> and B<sub>3</sub> reagents can be combined and reacted first to form an A<sub>2</sub>-B<sub>3</sub> moiety, followed by adding a C<sub>1</sub> reagent and completing polycondensation. The conditions for the synthesis can be determined by those having ordinary skill in the art. For example, the final step of the  
 10 reaction (reacting C<sub>1</sub> with the A<sub>2</sub>-B<sub>3</sub> moiety) can be conducted in the presence of a coupling agent such as carbodiimide.

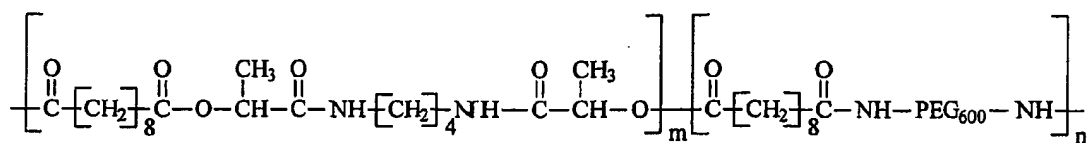
Optionally, instead of a C<sub>1</sub> diacid, a dichloride of the diacid can be used, for instance, sebacyl dichloride. In copolymer (X), the value of n can be between about 54 and about 96 and the value of m can be between about 4 and about 46, where m + n = 100.

15 Alternative versions of the copolymer (X) can be also synthesized to make the copolymer (X) harder. For example, an amino acid with shorter R<sub>2</sub> group or a shorter chain diamine (e.g., ethanediamine instead of 1,4-butanediamine) can be used for preparing the reagent A<sub>2</sub>.

Other possible methods of increasing the hardness of the copolymer (X) include using a shorter dicarboxylic acid C<sub>1</sub> (e.g., adipic acid instead of sebacic acid), or using PEG with lower  
 20 molecular weight, or reducing the proportion of the PEG-containing units in the overall copolymer (X).

Example 9

A copolymer having formula (XI) can be synthesized and used in practice of the invention.



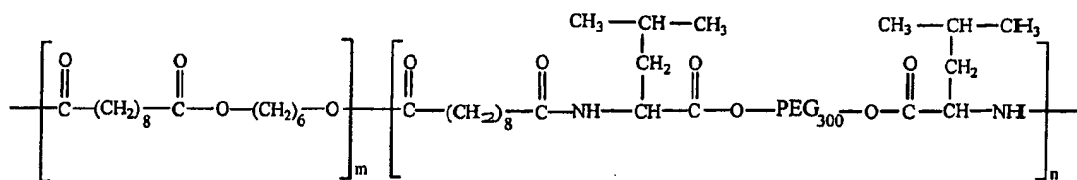
5

(XI)

The copolymer (XI) can be synthesized in same way as the copolymer (X) of Example 9, except that a reagent B<sub>4</sub> (such as PEG-diamine) shown in Table 4 can be used instead of a reagent B<sub>3</sub> (e.g., PEG-diol). PEG-diamine can be based on poly(ethylene glycol) having molecular weight of about 600 Daltons, which is symbolized by the abbreviation PEG<sub>600</sub>. In  
 10 copolymer (XI), the value of n can be between about 3 and about 35, and the value of m can be between about 97 and about 65, where m + n = 100.

Example 10

A copolymer having formula (XII) can be synthesized and used in practice of the invention.



15

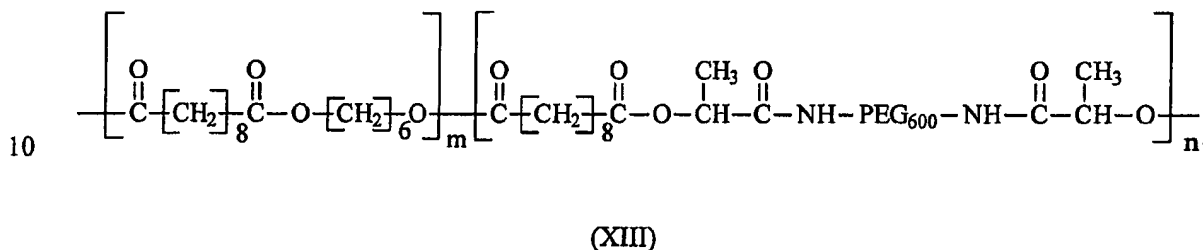
(XII)

The copolymer (XII) can be synthesized in same way as the copolymer (VIII) of Example

6, except that a reagent A<sub>3</sub> (diol) shown in Table 1 can be used instead of a reagent A<sub>2</sub> (amidediol), where X is (CH<sub>2</sub>)<sub>6</sub>. In other words, 1,6-hexanediol can be used as the reagent A<sub>3</sub>. A poly(ethylene glycol) moiety having molecular weight of about 300 Daltons can comprise a part of copolymer (XII), which is symbolized by the abbreviation PEG<sub>300</sub>. In copolymer (XII), the value of n can be between about 98 and about 71 and the value of m can be between about 2 and about 29, where m + n = 100.

### Example 11

A copolymer having formula (XIII) can be synthesized and used in practice of the invention.

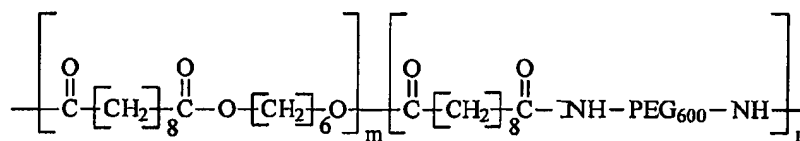


The copolymer (XIII) can be synthesized in same way as the copolymer (XII) of Example 10, except that a reagent B<sub>2</sub> (e.g., PEG-amidediol) shown in Table 4 can be used instead of a reagent B<sub>1</sub> (such as PEG-diester-diamine), where R<sub>2</sub> is methylethylene CH(CH<sub>3</sub>). In other words, B<sub>2</sub> can be synthesized by condensation of lactic acid with PEG-diamine shown as reagent B<sub>4</sub> in Table 4. PEG-diamine can be based on poly(ethylene glycol) having molecular weight of about 600 Daltons, which is symbolized by the abbreviation PEG<sub>600</sub>.

In copolymer (XIII), the value of n can be between about 98 and about 76 and the value of m can be between about 2 and about 24, where m + n = 100.

Example 12

A copolymer having formula (XIV) can be synthesized and used in practice of the invention.



5

(XIV)

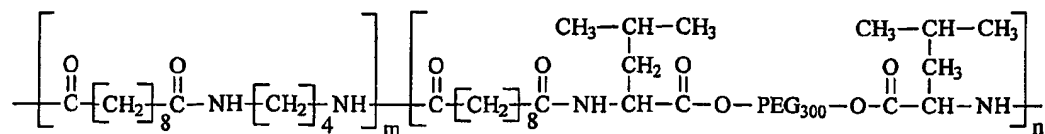
The copolymer (XIV) can be synthesized in same way as the copolymer (XIII) of Example 11, except that a reagent B<sub>4</sub> (e.g., PEG-diamine) as shown in Table 4 can be used instead of a reagent B<sub>2</sub> (such as PEG-amidediol). PEG-diamine can be based on poly(ethylene glycol) having molecular weight between about 300 and about 2,400 Daltons, for example, about 600 Daltons, which is symbolized by the abbreviation PEG<sub>600</sub>. Reagent A<sub>3</sub> (1,6-hexanediol) and reagent C<sub>1</sub> (sebacic acid) can be combined and reacted first to form an A<sub>3</sub>-C<sub>1</sub> moiety, followed by adding reagent B<sub>4</sub> and completing polycondensation. To facilitate the formation of the A<sub>3</sub>-C<sub>1</sub> moiety, sebacyl dichloride can be used as the C<sub>1</sub> reagent instead of sebacic acid. The conditions for the synthesis can be determined by those having ordinary skill in the art.

15 In copolymer (XIV), the value of n can be between about 98 and about 73 and the value of m can be between about 2 and about 27, where m + n = 100.

Example 13

A copolymer having formula (XV) can be synthesized and used in practice of the invention.





(XV)

The copolymer (XV) can be synthesized in same way as the copolymer (VIII) of Example 6, except that a reagent A<sub>4</sub> (diamine) shown in Table 1 can be used instead of a reagent A<sub>2</sub>

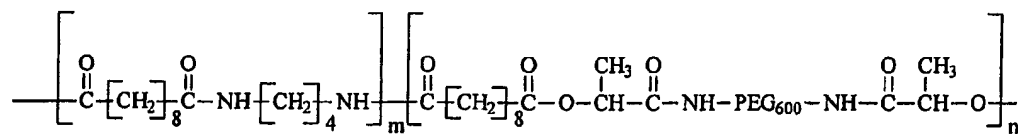
5 (amidediol), where Y is (CH<sub>2</sub>)<sub>4</sub>.

In other words, putrescine can be used as the reagent A<sub>4</sub>. A poly(ethylene glycol) moiety having molecular weight between about 300 Daltons and about 4,000 Daltons, for example, about 300 Daltons, can comprise a part of copolymer (XV), which is symbolized by the abbreviation PEG<sub>300</sub>.

10 In copolymer (XV), the value of n can be between about 98 and about 73 and the value of m can be between about 2 and about 27, where m + n = 100.

#### Example 14

A copolymer having formula (XVI) can be synthesized and used in practice of the invention.



(XVI)

The copolymer (XVI) can be synthesized in same way as the copolymer (IX) of Example

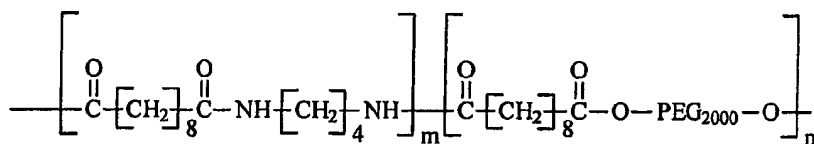
7, except that a reagent A<sub>4</sub> (diamine) shown in Table 1 can be used instead of a reagent A<sub>2</sub> (amidediol), where Y is (CH<sub>2</sub>)<sub>4</sub>. In other words, putrescine can be used as the reagent A<sub>4</sub>.

A poly(ethylene glycol) moiety having molecular weight between about 300 Daltons and about 4,000 Daltons, for example, about 600 Daltons, can comprise a part of copolymer (XVI),  
 5 which is symbolized by the abbreviation PEG<sub>600</sub>.

In copolymer (XVI), the value of n can be between about 98 and about 77, and the value of m can be between about 2 and about 23, where m + n = 100.

#### Example 15

A copolymer having formula (XVII) can be synthesized and used in practice of the  
 10 invention.



(XVII)

The copolymer (XVII) can be synthesized in same way as the copolymer (X) of Example 8, except that a reagent A<sub>4</sub> (diamine) shown in Table 1 can be used instead of a reagent A<sub>2</sub> (amidediol), where Y is (CH<sub>2</sub>)<sub>4</sub>. In other words, putrescine can be used as the reagent A<sub>4</sub>.  
 15

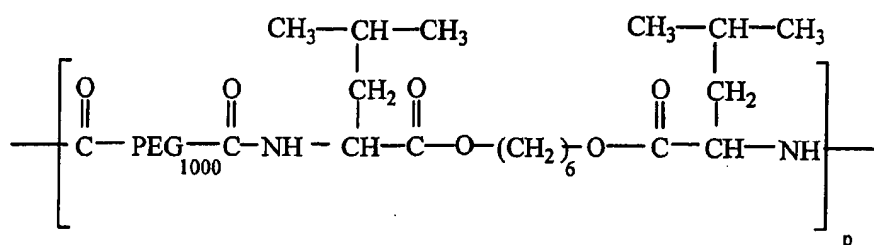
A poly(ethylene glycol) moiety having molecular weight between about 300 Daltons and about 4,000 Daltons, for example, about 2,000 Daltons can comprise a part of copolymer (XVII), which is symbolized by the abbreviation PEG<sub>2000</sub>.

In copolymer (XVII), the value of n can be between about 995 about 910 the value of m

can be between about 5 and about 90, where  $m + n = 1000$ .

### Example 16

A copolymer having formula (XVIII) can be synthesized and used in practice of the invention.

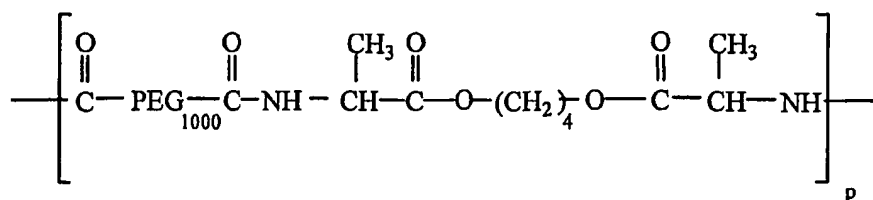


(XVIII)

To synthesize the copolymer (XVIII), reagents  $A_1$  and  $C_2$  can be combined in the molar ratio of about 1:1 and copolymerized. The conditions for the synthesis can be determined by those having ordinary skill in the art.  $A_1$  can be a diol-diamine shown in Table 1, where  $R_1$  is  $i$ -C<sub>4</sub>H<sub>9</sub> and X is (CH<sub>2</sub>)<sub>6</sub>. In other words,  $A_1$  can be synthesized by condensation of leucine with 1,6-hexanediol.  $C_2$  can be a PEG-dicarboxylic acid shown in Table 5, derived from poly(ethylene glycol) having molecular weight of about 1,000 Daltons, which is symbolized by the abbreviation PEG<sub>1000</sub>. A total molecular weight of the copolymer (XVIII) can be between about 20,000 Daltons and about 50,000 Daltons. The value of the integer  $p$  can be between about 14 and about 360.

### Example 17

A copolymer having formula (XIX) can be synthesized and used in practice of the invention.



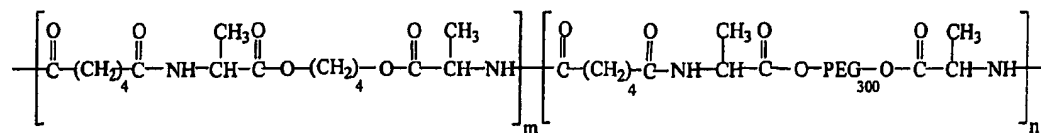
(XIX)

The copolymer (XIX) can be synthesized in same way as the copolymer (XVIII) of Example 16, except that a reagent A<sub>2</sub> (amidediol) shown in Table 1 can be used instead of a  
 5 reagent A<sub>1</sub> (diol-diamine), where R<sub>2</sub> is methylenemethylene CH(CH<sub>3</sub>), and Y is (CH<sub>2</sub>)<sub>4</sub>. In other words, A<sub>2</sub> can be synthesized by condensation of lactic acid with putrescine. C<sub>2</sub> can be a PEG-dicarboxylic acid shown in Table 5 derived from poly(ethylene glycol) having molecular weight of about 1,000 Daltons, which is symbolized by the abbreviation PEG<sub>1000</sub>.

A total molecular weight of the copolymer (XIX) can be between about 20,000 Daltons  
 10 and about 50,000 Daltons. The value of the integer p can be between about 15 and about 390.

### Example 18

Co-poly-{[N,N'-adipoyl-bis-(L-alanine)-1,4-butylene diester]<sub>37</sub>-[N,N'-adipoyl-bis-(L-alanine)-PEG300 diester]<sub>67</sub>} having formula (XX) can be synthesized and used in practice of the invention. This copolymer belongs to category (A), type A<sub>1</sub>-B<sub>1</sub>-C<sub>1</sub>, described above.



(XX)

To synthesize the copolymer (XX), about 41 ml (about 0.293 mole) dry triethylamine in about 75 ml dry solvent N,N'-dimethylacetamide, at room temperature, can be added to a mixture of:

(a) about 28.64 g (about 0.0497 mole) di-*para*-toluenesulfonic acid salt of *bis*-(L-alanine)-1,4-butylene diester;

(b) about 65.57 g (about 0.0834 mole) di-*para*-toluenesulphonic acid salt of *bis*-(L-alanine)-PEG300 diester; and

(c) about 51.62 g (about 0.1331 mole) di-*para*-nitrophenyl adipate.

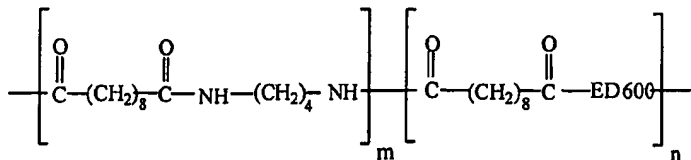
The mixture can be stirred until full dissolution and then the temperature can be raised to about 80°C. After stirring for about 24 hours, the viscous mixture can be cooled to room temperature, diluted with about 100 ml ethanol, and precipitated into an excess of water. The separated polymer can be thoroughly washed with water, spread thinly onto a TEFLON pan, and dried at room temperature under vacuum (about 70 mm Hg) for about 24 hours.

As amide bonds are formed in the presence of existing ester bonds, mild conditions need to be used, and this will be understood by those having ordinary skill in the art. For example, polymerization techniques using good leaving groups such as *para*-nitrophenol or carboxyl groups activated by carbodiimides can be used. In this invention, the range of stoichiometries can be determined by the desired mass content of PEG.

For example, the final polymer can contain between about 5 mass % and about 50 mass % of PEG. For copolymer (XX), this corresponds to molar ratios of the two blocks of (alanine/butanediol-adipic acid) (A<sub>1</sub>-C<sub>1</sub> blocks) and (alanine/PEG-adipic acid) (B<sub>1</sub>-C<sub>1</sub> blocks) between about 94:6 and about 12:88.

Example 19

Co-poly- $\{[N,N'$ -sebacyl-1,4-butylene diamide] $_{86}$ - $[N,N'$ -sebacyl-(ED-600) diamide] $_{14}\}$  having formula (XXI) can be synthesized and used in practice of the invention. This copolymer belongs to category (B), type (A<sub>4</sub>-B<sub>4</sub>-C<sub>1</sub>), described above.



5

(XXI)

In formula (XXI), "ED-600" is an abbreviation symbolizing JEFFAMINE ED-600 polymer described above (see Example 4).

To synthesize the copolymer (XXI), about 104 ml (about 0.744 mole) dry triethylamine in about 65 ml dry solvent N,N'-dimethylacetamide, at room temperature, can be added to a mixture of:

10

(a) about 23.38 g (about 0.266 mole) dry 1,4-diaminobutane; and

(b) about 25 g (about 0.0417 mole) dry ED-600.

The mixture can be stirred, under a nitrogen atmosphere at room temperature, until full dissolution. The mixture can be cooled in ice water and about 80.75 g (about 0.338 mole) sebacoyl chloride can be added dropwise with stirring. The solution can be allowed to come to ambient temperature with stirring stirred continued overnight. The viscous mixture can then be precipitated into an excess of water. The separated polymer can be thoroughly washed with

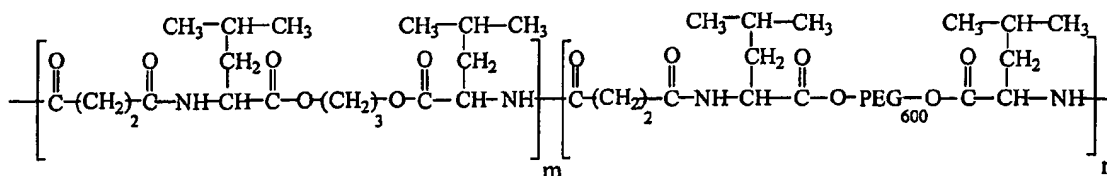
15

water, spread thinly into a TEFLON pan, and dried at room temperature under vacuum (about 70 mm Hg) for about 24 hours.

As only amide bonds are present, without any other hydrolysable groups, harsher synthetic conditions can be used for this category as understood by those having ordinary skill in the art. For example, acid chlorides can be used. The mass contents of PEG in the final copolymer (XXI) can be between about 5 mass % and about 50 mass %. For copolymer (XXI), this corresponds to molar ratios of the two blocks of diamine-sebacic acid (A<sub>4</sub>-C<sub>1</sub> blocks) and ED-600-sebacic acid (B<sub>4</sub>-C<sub>1</sub> blocks) of between about 97:3 and about 57:43.

#### Example 20

Co-poly- $\{[N,N'$ -succinyl-*bis*-(L-leucine)-1,3-propylene diester]<sub>82</sub>-[succinyl-PEG<sub>600</sub> diester]<sub>18</sub> $\}$  having formula (XXII) can be synthesized and used in practice of the invention. This copolymer belongs to category (C), type (A<sub>1</sub>-B<sub>3</sub>-C<sub>1</sub>), described above.



(XXII)

To synthesize the copolymer (XXII), about 26.8 g (about 0.227 mole) succinic acid, and about 52.3 g (about 0.454 mole) N-hydroxysuccinimide can be added to about 100 ml dry N,N'-dimethylformamide at room temperature under nitrogen and dissolved with stirring. About 93.67 g (about 0.454 mole) dicyclohexylcarbodiimide (DCC) can be to the mixture added, and the mixture can be allowed to stir for about 16 hours at room temperature.

The reaction mixture can be filtered through filter paper to remove the urea byproduct, and the solution can be placed into a reaction flask. The following compounds can then be added to the reaction mixture with continued stirring:

(a) about 55.9 g (about 0.185 mole) the free base of *bis*-(L-leucine)-1,3-propylene diester;  
5 and

(b) about 25 g (about 0.0417 mole) poly(ethylene glycol) having molecular weight of about 600 Daltons (PEG600).

The mixture can be stirred at room temperature for about 2 hours and then the temperature can be increased to about 60°C and stirred for about two more hours. The polymer  
10 can precipitated by adding the reaction solution dropwise to about 2 liters of ethyl acetate with stirring. The precipitated polymer can be placed as a thin layer into a TEFLON pan and dried at room temperature under vacuum (about 70 mm Hg) for about 24 hours.

In this category, both amide and ester bonds are present in the copolymer. Accordingly, mild conditions need to be used, as understood by those having ordinary skill in the art. For  
15 example, carboxylate groups activated by carbodiimides can be used or good leaving groups such as *para*-nitro-phenol can be used. The mass contents of PEG in the final copolymer (XXII) can be between about 5 mass % and about 50 mass %. For copolymer (XXII), this corresponds to molar ratios of the two blocks of leucine/propanediol-succinic acid (A<sub>1</sub>-C<sub>1</sub> blocks) and PEG-diol-succinic acid (B<sub>3</sub>-C<sub>1</sub> blocks) between about 94:6 and about 12:88.

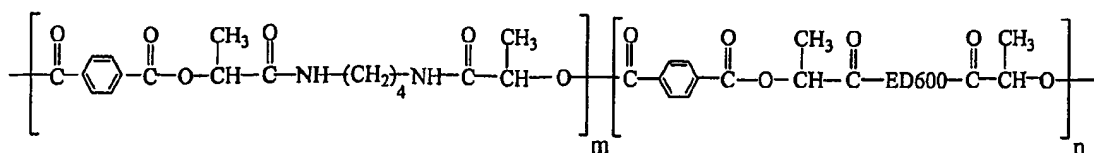
20

#### Example 21

Co-poly-{{terephthalyl-*bis*-(D,L-lactate)-1,4-butylene diamide}<sub>81</sub>-[terphthalyl-*bis*-(glycolate)-ED600 diamide]<sub>19</sub>} having formula (XXIII) can be synthesized and used in practice of



the invention. This copolymer belongs to category (D), type (A<sub>2</sub>-B<sub>2</sub>-C<sub>1</sub>), described above.



(XXIII)

To synthesize the copolymer (XXIII), the following compounds can be combined in a reaction flask equipped with nitrogen atmosphere, vacuum port, and heating mantle:

- (a) about 0.12 g (about  $3.5 \times 10^{-4}$  moles) titanium tetrabutoxide;
- (b) about 41.2 g (about 0.178 mole) *bis*-(D,L-lactate)-1,4-butylene diamide;
- (c) about 29.83 g (about 0.0417 mole) *bis*-(glycolate)-ED600 diamide, where(ED-600 is as described above; and
- (d) about 42.6 g (about 0.219 mole) dimethyl terephthalate.

The flask can be sealed and heated to about 180°C for about 2 hours. After about 2 hours, the pressure can be reduced to about 0.1 Torr, and the solution can be maintained at about 180°C for about two more hours.

In this category, only ester bonds present in the copolymer. Amide bonds may, or may not, be present in the reagents. Accordingly, transesterification reactions, under dehydrating conditions, in the presence of the Lewis or Bronsted acid catalysts can be used. Use of acid chlorides is also a viable synthetic technique, because the only hydrolysable bonds that may be present in the reagents are stable amide bonds. The mass contents of PEG in the final copolymer

(XXIII) can be between about 5 mass % and about 50 mass %. For copolymer (XXIII), this corresponds to molar ratios of the two blocks of (A<sub>2</sub>-C<sub>1</sub> blocks) (B<sub>2</sub>-C<sub>1</sub> blocks) between about 97:3 and about 49:51.

#### Example 22

5 A first composition can be prepared, the composition including:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass % copoly- {[N,N'-sebacoyl-bis-(L-leucine)-1,6-hexylene diester]<sub>75</sub>-[N,N'-sebacoyl-L-lysine benzyl ester]<sub>25</sub>};

(b) between about 0.1 mass % and about 2.0 mass %, for example, about 0.5 mass%  
10 paclitaxel; and

(c) the balance, a solvent blend of ethanol and 1,1,2-trichloroethane, where the mass ratio between ethanol and 1,1,2-trichloroethane can be about 1:1.

The first composition can be applied onto the surface of bare 12 mm VISION stent (available from Guidant Corporation). Coating can be sprayed and dried to form a drug-polymer  
15 layer. A spray coater can be used having a 0.014 round nozzle maintained at ambient temperature with a feed pressure of about 2.5 psi (0.17 atm) and an atomization pressure of about 15 psi (1.02 atm). Coating can be applied at about 20 µg per pass. Between the passes the stent can be dried for about 10 seconds in a flowing air stream at about 50°C. About 270 µg of wet coating can be applied. The stent can be baked at about 50°C for about one hour, yielding a  
20 drug-polymer layer containing about 250 µg of dry coating.

A second composition can be prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass % copolymer (XXX) described in Example 18; and

(b) the balance, a solvent blend of ethanol and 1,1,2-trichloroethane, where the mass ratio  
5 between ethanol and 1,1,2-trichloroethane can be about 1:1.

The second composition can be applied onto the dry drug-polymer layer to form the topcoat layer. The same spraying technique and equipment can be used for the applying the topcoat layer as described for the drug-polymer layer. About 120 µg of wet coating can be applied, followed by drying, e.g., baking at about 50°C for about one hour, yielding about 100 µg  
10 of a biocompatible topcoat layer.

#### Example 23

A first composition can be prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass% copolymer co-poly- $\{[N,N'$ -sebacoyl-bis-(L-leucine)-1,6-hexylene diester]<sub>75</sub>-[N,N'-sebacoyl-L-  
15 lysine-4-amino-TEMPO amide]<sub>25</sub>}; and

(b) the balance, 100% ethanol.

The first composition can be applied onto the surface of bare 12 mm VISION stent using equipment and coating technique described in Example 22. About 120 µg of wet coating can be applied. The stents can be baked at about 50°C for about one hour, yielding about 100 µg of a  
20 dry primer layer. The copolymer forming the primer layer includes 4-amino-TEMPO (4-amino-2,2',6,6'-tetramethylpiperidine-1-oxy) moiety attached to lysine via an amide linkage.

A second composition can be prepared by mixing the following components:

(a) between about 0.1 mass % and about 3.0 mass %, for example, about 2.0 mass% EVEROLIMUS; and

(b) the balance, 100% ethanol.

5       The second composition can be applied onto the dry primer layer, to form the pure drug layer. The same spraying technique and equipment can be used for the applying the drug layer as described above. Coating can be applied at about 20 µg per pass. Between the passes the stent can be dried for about 10 seconds in a flowing air stream at about 50°C. About 110 µg of neat drug coating can be applied. The stent can be baked at about 50°C for about one hour, yielding a  
10   pure dry drug- layer containing about 100 µg of dry coating.

A third composition can be prepared by mixing the following components:

(a) between about 0.5 mass % and about 10 mass %, for example, about 1.0 mass % copolymer (XX) described in Example 18;

(b) between about 0.5 mass % and about 10 mass %, for example, about 1.0 mass % co-  
15   poly- {[N,N'-sebacoyl-bis-(L-leucine)-1,6-hexylene diester]<sub>75</sub>-[N,N'-sebacoyl-L-lysine benzyl ester]<sub>25</sub>} described in Example 22; and

(c) the balance, 100% ethanol.

The third composition can be applied onto the dry pure drug layer to form the topcoat layer. The same spraying technique and equipment can be used for the applying the topcoat layer  
20   as described above. About 440 µg of wet coating can be applied, followed by drying, e.g.,

baking at about 50°C for about one hour, yielding about 400 µg of a biocompatible topcoat layer, which can also control the release of the drug.

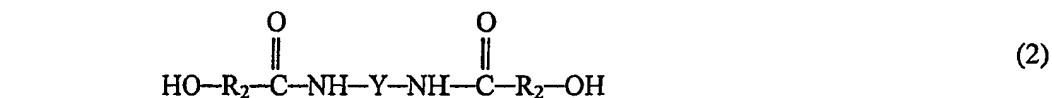
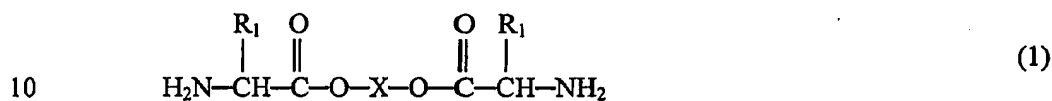
While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without  
5 departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

## CLAIMS

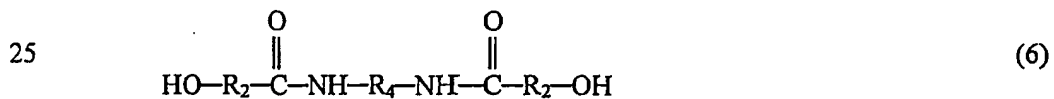
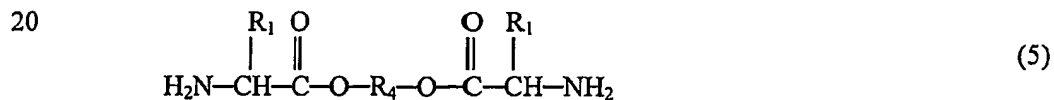
## WHAT IS CLAIMED IS:

1. A medical article comprising an implantable substrate having a coating, the coating including a polymeric product of a reaction between a first reagent, a second reagent, and  
 5 a third reagent, wherein:

(a) the first reagent is selected from a group consisting of compounds having formulae (1), (2), (3), and (4):



(b) the second reagent is selected from a group consisting of compounds having formulae (5), (6), (7), and (8):



(c) the third reagent is a dicarboxylic acid having the formula (9):



5

wherein:

$\text{R}_1$  is a hydrogen, methyl, *iso*-propyl, *sec*-butyl, *iso*-butyl, or benzyl group;

$\text{R}_2$  is methylene, methylenemethylene, *n*-propylene, *iso*-propylene, ethylenemethylene, *n*-butylene, *iso*-butylene, *sec*-butylene, or *n*-amylene group;

10  $\text{R}_3$  is a straight chained or branched aliphatic alkylene group  $\text{C}_n\text{H}_{2n}$ , wherein  $n$  is an integer between 2 and 12;

$\text{R}_4$  is a moiety derived from a compound selected from a group consisting of poly(ethylene glycol), poly(propylene glycol), random poly(ethylene glycol-co-propylene glycol), poly(ethylene glycol)-block-poly(propylene glycol), hyaluronic acid, poly(2-hydroxyethyl  
15 methacrylate), poly(3-hydroxypropylmethacrylamide), poly(styrene sulfonate), poly(vinyl pyrrolidone), and cellulose;

$\text{X}$  is a straight chained or branched aliphatic alkylene group  $\text{C}_n\text{H}_{2n}$ , wherein  $n$  is an integer between 2 and 12; and

$\text{Y}$  is a straight chained or branched aliphatic alkylene group  $\text{C}_n\text{H}_{2n}$ , wherein  $n$  is 1, 2, or 5.

20 2. The medical article of Claim 1, wherein the implantable substrate is a stent.

3. The medical article of Claim 1, wherein the compound of formula (1) is a diol-diamine, the diol-diamine is a product of condensation of an amino acid and a diol.

4. The medical article of Claim 3, wherein the amino acid has the formula (10):



5. The medical article of Claim 3, wherein the amino acid is selected from a group consisting of glycine, alanine, valine, isoleucine, leucine, and phenyl alanine.

- 5          6. The medical article of Claim 3, wherein a diol is selected from a group consisting of ethylene glycol, 1,3-propanediol, 1,4-butane diol, 1,5-pentanediol, 1,6-hexanediol, 1,7-heptanediol, 1,8-octanediol, 1,9-nonanediol, 1,10-decanediol, 1,11-undecanediol, and 1,12-dodecanediol.

7. The medical article of Claim 1, wherein the compound of formula (2) is an  
10 amidediol, the amidediol is a product of condensation of a hydroxy acid and a diamine.

8. The medical article of Claim 7, wherein the hydroxy acid has the formula (11):



9. The medical article of Claim 7, wherein the hydroxy acid is selected from a group consisting of glycolic acid, lactic acid,  $\beta$ -hydroxybutyric acid,  $\alpha$ -hydroxyvaleric acid, and  $\epsilon$ -  
15 hydroxycaproic acid.

10. The medical article of Claim 7, wherein the diamine is selected from a group consisting of putrescine, 1,2-ethanediamine, and cadavarene.

11. The medical article of Claim 1, wherein the compound of formula (3) is selected from a group consisting of ethylene glycol, 1,3-propanediol, 1,4-butane diol, 1,5-pentanediol,  
20 1,6-hexanediol, 1,7-heptanediol, 1,8-octanediol, 1,9-nonanediol, 1,10-decanediol, 1,11-undecanediol, and 1,12-dodecanediol.



12. The medical article of Claim 1, wherein the compound of formula (4) is selected from a group consisting of putrescine, 1,2-ethanediamine, and cadavarene.

13. The medical article of Claim 1, wherein the compound of formula (5) is a PEG-diester-diamine conjugate, the conjugate is a product of condensation of an amino acid and  
5 poly(ethylene glycol).

14. The medical article of Claim 13, wherein the amino acid has the formula (10):



15. The medical article of Claim 13, wherein the amino acid is selected from a group consisting of glycine, alanine, valine, isoleucine, leucine, phenyl alanine, tyrosine, serine, and  
10 glutamic acid.

16. The medical article of Claim 1, wherein the compound of formula (6) is a PEG-amidediol conjugate, the conjugate is a product of condensation of a hydroxy acid and PEG-diamine.

17. The medical article of Claim 16, wherein the hydroxy acid has the formula (11):



18. The medical article of Claim 17, wherein the hydroxy acid is selected from a group consisting of glycolic acid, lactic acid,  $\beta$ -hydroxybutyric acid,  $\alpha$ -hydroxyvaleric acid, and  $\epsilon$ -hydroxycaproic acid.

19. A medical article comprising an implantable substrate having a coating, the  
20 coating including a copolymer having a general formula (12) or (13):

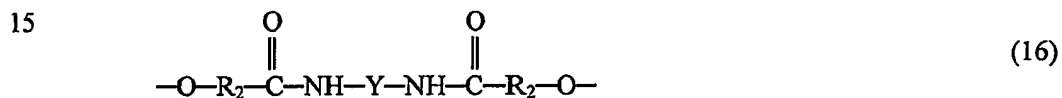
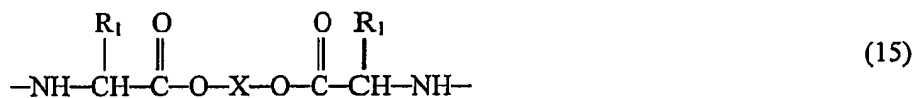


wherein:

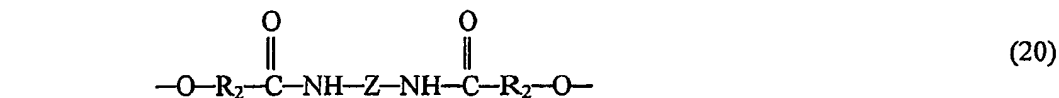
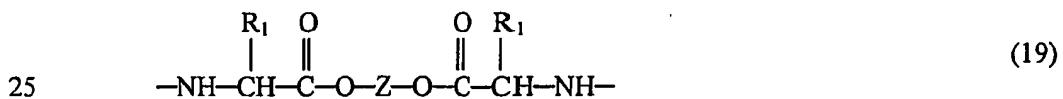
M is a moiety represented by the structure having the formula (14)



P is a moiety selected from a group consisting of structures having the formulae (15), (16),  
 10 (17), and (18):



Q is a moiety selected from a group consisting of structures having the formulae (19),  
 (20), and (21):





M<sub>1</sub> is a moiety represented by the structure having the formula (22):



R<sub>1</sub> is hydrogen, methyl, *iso*-propyl, *sec*-butyl, *iso*-butyl, or benzyl group;

R<sub>2</sub> is methylene, methylenemethylene, *n*-propylene, *iso*-propylene, ethylenemethylene, *n*-butylene, *iso*-butylene, *sec*-butylene, or *n*-amylene group;

R<sub>3</sub> is a straight chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is an integer between 2 and 12;

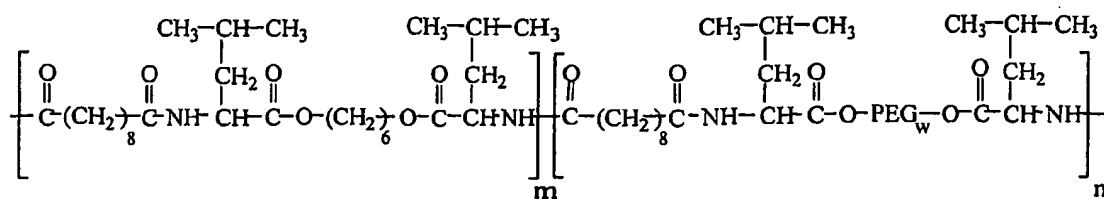
X is a straight chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is an integer between 2 and 12;

Y is a straight chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is 1, 2, or 5;

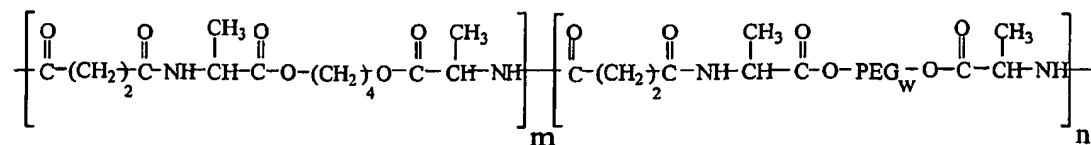
Z is a moiety derived from a compound selected from a group consisting of poly(ethylene glycol), poly(propylene glycol), random poly(ethylene glycol-co-propylene glycol), poly(ethylene glycol)-block-poly(propylene glycol), hyaluronic acid, poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropylmethacrylamide), poly(styrene sulfonate), poly(vinyl pyrrolidone), and cellulose; and

m, n, and p are integers where the value of m is between 5 and 1,800, the value of n is between 1 and 800 and the value of p is between 4 and 1,500.

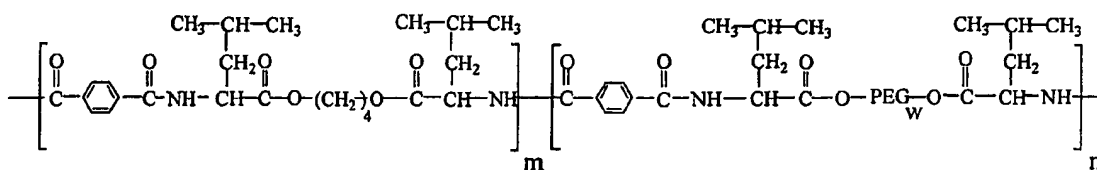
20. The medical article of Claim 19, wherein the polymer is selected from a group consisting of copolymers of formulae (23), (24), (25), (26), (27), (28), (29), (30), (31), (32), (33), (34), (35), (36), (37), (38), (39), (40), (41), (42), and (43):



(23),

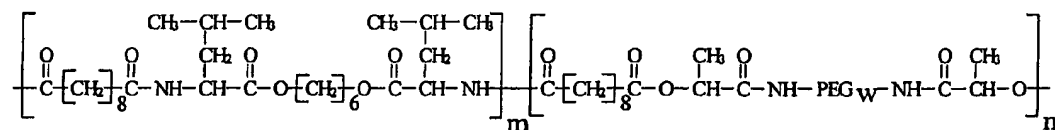


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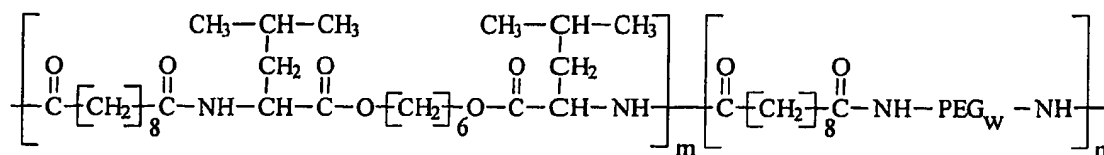


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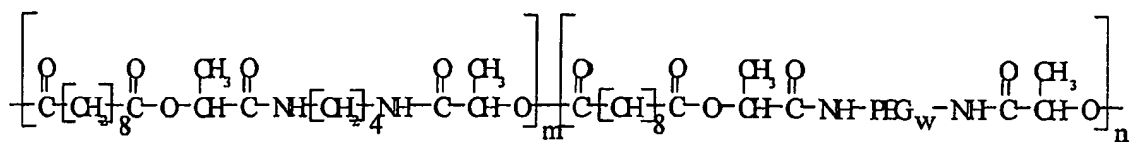


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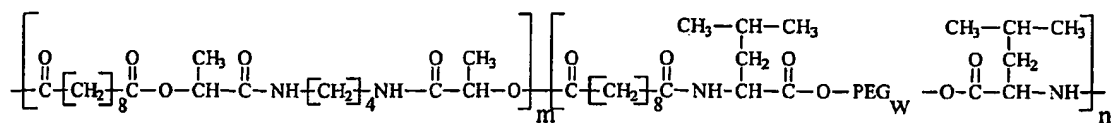


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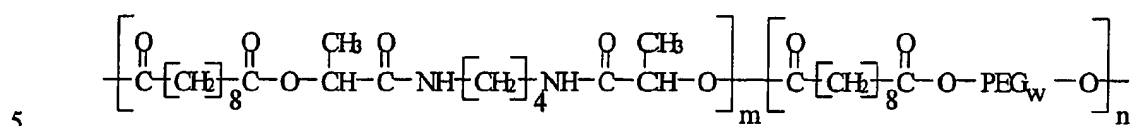
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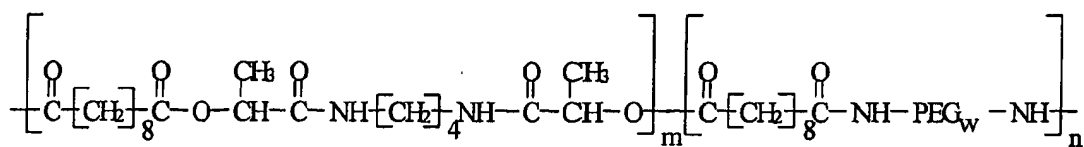
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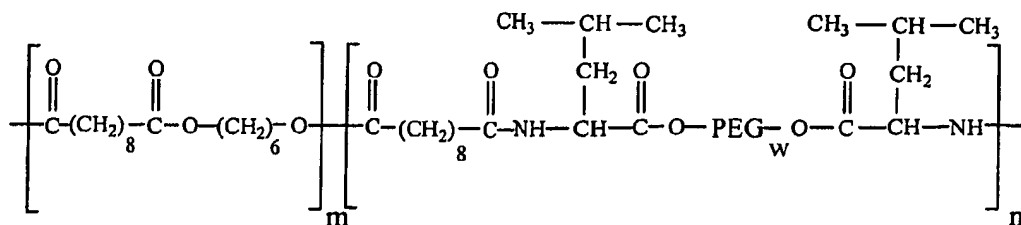
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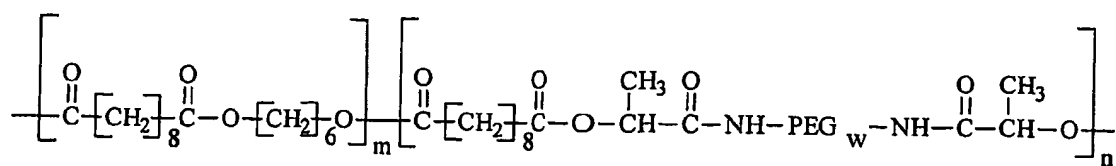
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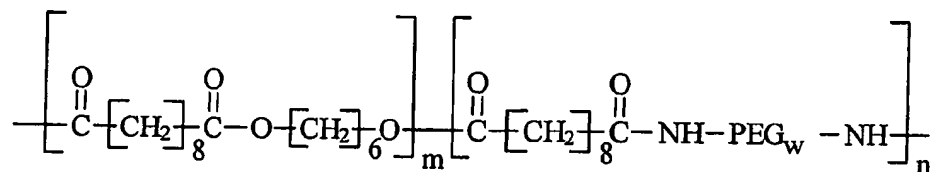
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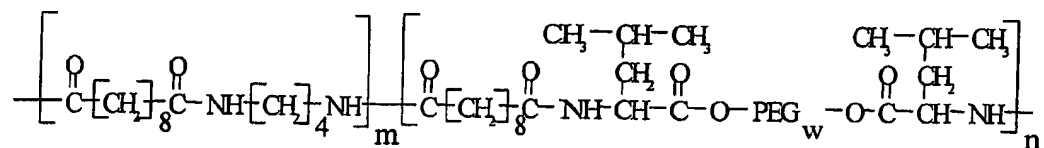
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(33),

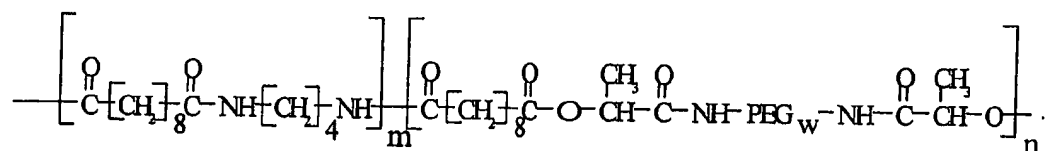


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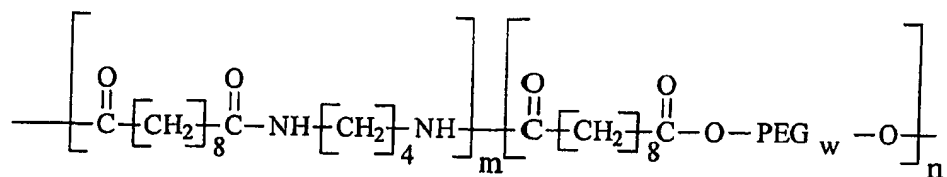


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(35),

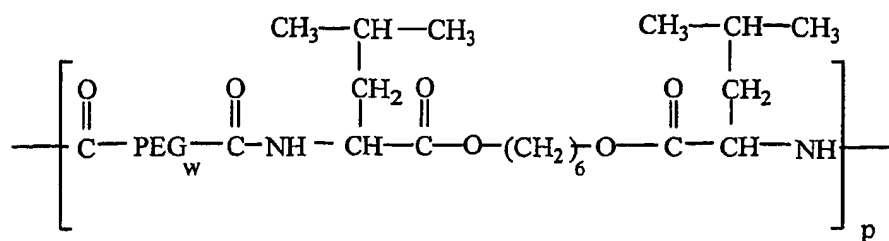


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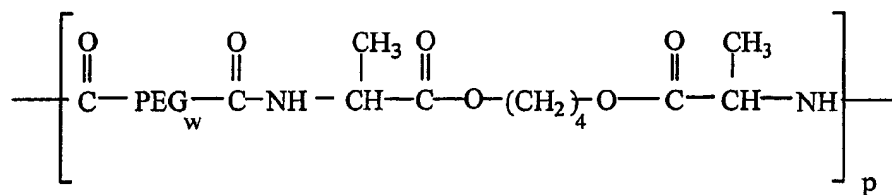


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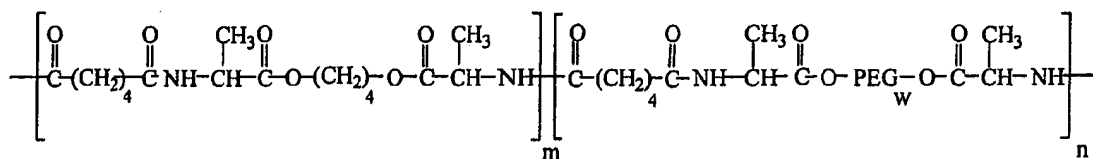
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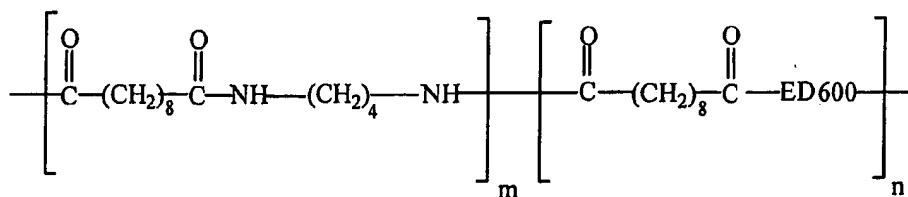
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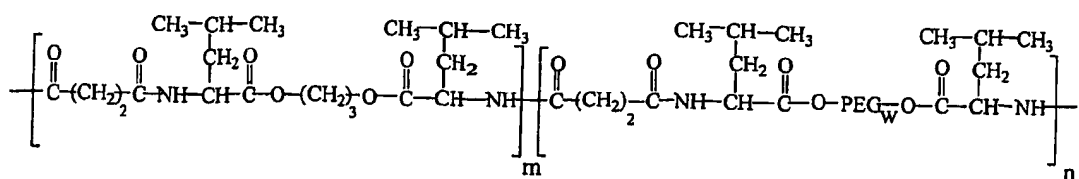
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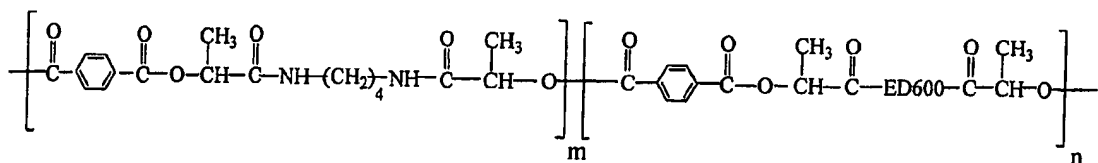
(40),



(41),



(42), and

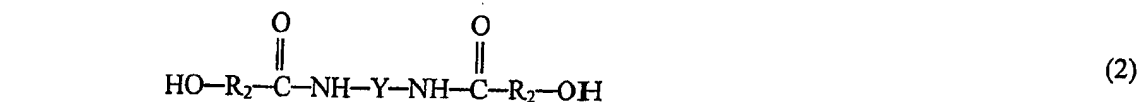
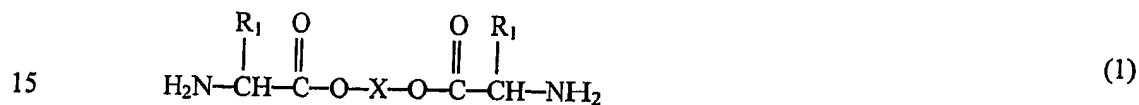


(43);

- 5 where m and n are integers, and w is a molecular weight ranging from about 100 to about 4,000 Daltons.

21. A method for fabricating a medical article, the method including synthesizing a copolymer and forming a coating based on the copolymer on at least a portion of an implantable substrate, the synthesizing of the copolymer including reacting a first reagent with a second  
10 reagent and with a third reagent, wherein:

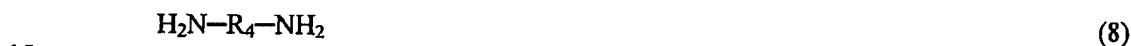
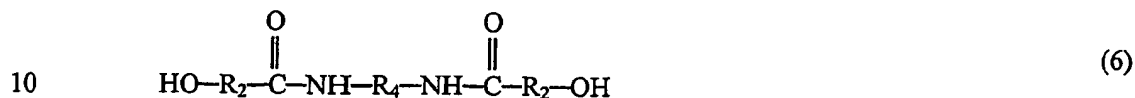
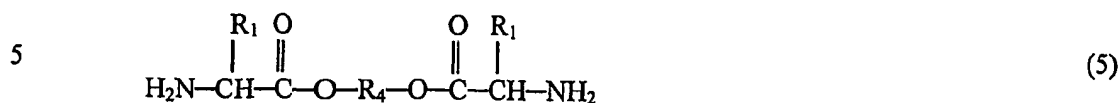
- (a) the first reagent is selected from a group consisting of compounds having formulae (1), (2), (3), and (4):







(b) the second reagent is selected from a group consisting of compounds having formulae (5), (6), (7), and (8):



(c) the third reagent is a dicarboxylic acid having the formula (9):



wherein:

R<sub>1</sub> is hydrogen, methyl, *iso*-propyl, *sec*-butyl; *iso*-butyl, or benzyl group;

R<sub>2</sub> is methylene, methylenemethylene, *n*-propylene, *iso*-propylene, ethylenemethylene, *n*-butylene, *iso*-butylene, *sec*-butylene, or *n*-amylene group;

R<sub>3</sub> is a straight chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is an integer between 2 and 12;

R<sub>4</sub> is a moiety derived from a compound selected from a group consisting of poly(ethylene glycol), poly(propylene glycol), random poly(ethylene glycol-co-propylene glycol), poly(ethylene glycol)-block-poly(propylene glycol), hyaluronic acid, poly(2-hydroxyethyl

methacrylate), poly(3-hydroxypropylmethacrylamide), poly(styrene sulfonate), poly(vinyl pyrrolidone), and cellulosics;

X is a straight chained or branched aliphatic alkylene group  $C_nH_{2n}$ , wherein n is an integer between 2 and 12; and

5 Y is a straight chained or branched aliphatic alkylene group  $C_nH_{2n}$ , wherein n is 1, 2, or 5.

22. The method of Claim 21, wherein the implantable substrate is a stent.

23. The method of Claim 21, wherein the molar ratio between the first reagent, the second reagent, and the third reagent is about 1:1:2.

24. The method of Claim 21, wherein the compound of formula (1) is a diol-diamine,  
10 the diol-diamine is a product of condensation of an amino acid and a diol.

25. The method of Claim 24, wherein the amino acid has the formula (10):



26. The method of Claim 24, wherein the amino acid is selected from a group consisting of glycine, alanine, valine, isoleucine, leucine, and phenyl alanine.

15 27. The method of Claim 24, wherein a diol is selected from a group consisting of ethylene glycol, 1,3-propanediol, 1,4-butane diol, 1,5-pentanediol, 1,6-hexanediol, 1,7-heptanediol, 1,8-octanediol, 1,9-nonanediol, 1,10-decanediol, 1,11-undecanediol, and 1,12-dodecanediol.

28. The method of Claim 21, wherein the compound of formula (2) is an amidediol,  
20 the amidediol is a product of condensation of a hydroxy acid and a diamine.

29. The method article of Claim 28, wherein the hydroxy acid has the formula (11):



30. The method of Claim 28, wherein the hydroxy acid is selected from a group consisting of glycolic acid, lactic acid,  $\beta$ -hydroxybutyric acid,  $\alpha$ -hydroxyvaleric acid, and  $\epsilon$ -  
5 hydroxycaproic acid.

31. The method of Claim 28, wherein the diamine is selected from a group consisting of putrescine, 1,2-ethanediamine, and cadavarene.

32. The method of Claim 21, wherein the compound of formula (3) is selected from a group consisting of ethylene glycol, 1,3-propanediol, 1,4-butane diol, 1,5-pentanediol, 1,6-  
10 hexanediol, 1,7-heptanediol, 1,8-octanediol, 1,9-nonanediol, 1,10-decanediol, 1,11-undecanediol, and 1,12-dodecanediol.

33. The method of Claim 21, wherein the compound of formula (4) is selected from a group consisting of putrescine, 1,2-ethanediamine, and cadavarene.

34. The method of Claim 21, wherein the compound of formula (5) is a PEG-diester-  
15 diamine conjugate, the conjugate is a product of condensation of an amino acid and poly(ethylene glycol).

35. The method of Claim 34, wherein the amino acid has the formula (10):



36. The method of Claim 34, wherein the amino acid is selected from a group  
20 consisting of glycine, alanine, valine, isoleucine, leucine, phenyl alanine, tyrosine, serine, and glutamic acid.

37. The method of Claim 21, wherein the compound of formula (6) is a PEG-amidediol conjugate, the conjugate is a product of condensation of a hydroxy acid and PEG-diamine.

38. The method of Claim 37, wherein the hydroxy acid has the formula (11):



39. The method of Claim 37, wherein the hydroxy acid is selected from a group consisting of glycolic acid, lactic acid,  $\beta$ -hydroxybutyric acid,  $\alpha$ -hydroxyvaleric acid, and  $\epsilon$ -hydroxycaproic acid.

40. A method for fabricating a medical article, the method including synthesizing a  
10 copolymer and forming a coating based on the copolymer on at least a portion of an implantable substrate, wherein the copolymer has a general formula (12) or (13):

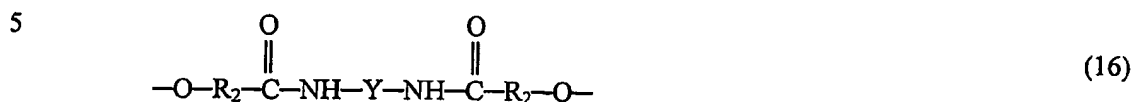


wherein:

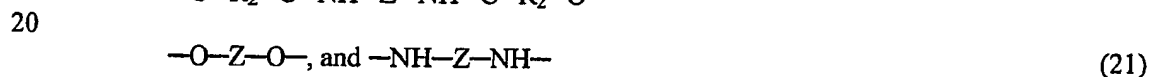
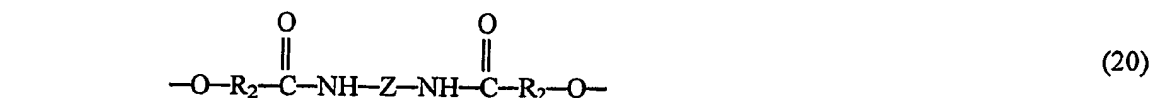
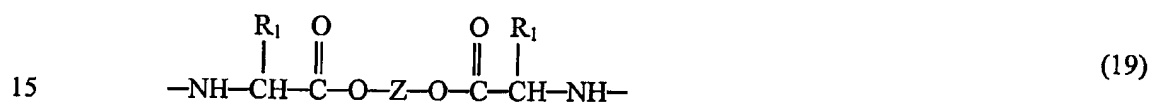
15            M is a moiety represented by the structure having the formula (14)



P is a moiety selected from a group consisting of structures having the formulae (15), (16),  
20 (17), and (18):



Q is a moiety selected from a group consisting of structures having the formulae (19), (20), and (21):



M<sub>1</sub> is a moiety represented by the structure having the formula (22):



R<sub>1</sub> is hydrogen, methyl, *iso*-propyl, *sec*-butyl; *iso*-butyl, or benzyl group;

R<sub>2</sub> is methylene, methylenemethylene, *n*-propylene, *iso*-propylene, ethylenemethylene, *n*-butylene, *iso*-butylene, *sec*-butylene, or *n*-amylene group;

R<sub>3</sub> is a straight chained or branched aliphatic alkylene group C<sub>n</sub>H<sub>2n</sub>, wherein n is an integer between 2 and 12;

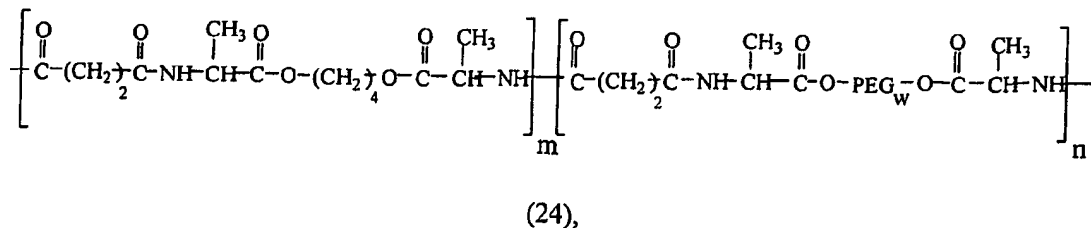
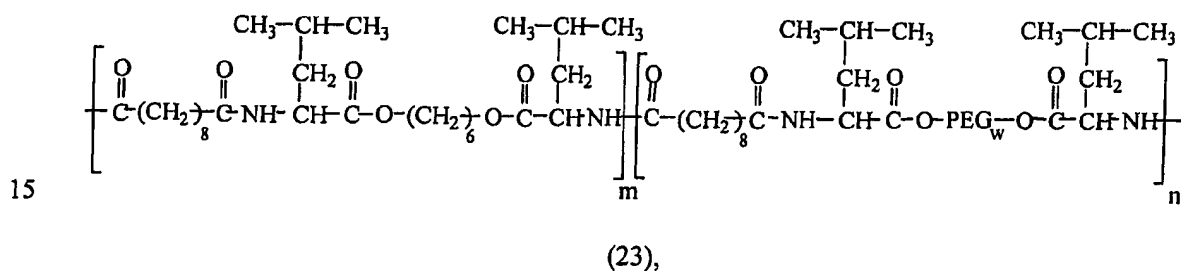
X is a straight chained or branched aliphatic alkylene group  $C_nH_{2n}$ , wherein n is an integer between 2 and 12;

Y is a straight chained or branched aliphatic alkylene group  $C_nH_{2n}$ , wherein n is 1, 2, or 5;  
and

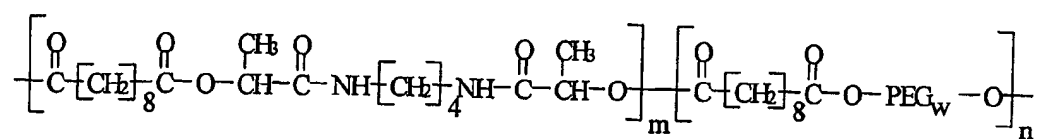
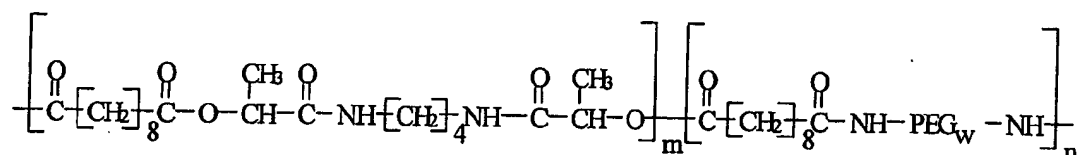
5 Z is a moiety derived from a compound selected from a group consisting of poly(ethylene glycol), poly(propylene glycol), random poly(ethylene glycol-co-propylene glycol), poly(ethylene glycol)-block-poly(propylene glycol), hyaluronic acid, poly(2-hydroxyethyl methacrylate), poly(3-hydroxypropylmethacrylamide), poly(styrene sulfonate), poly(vinyl pyrrolidone), and cellulose; and

10 m, n, and p are integers where the value of m is between 5 and 1,800, the value of n is between 1 and 800 and the value of p is between 4 and 1,500.

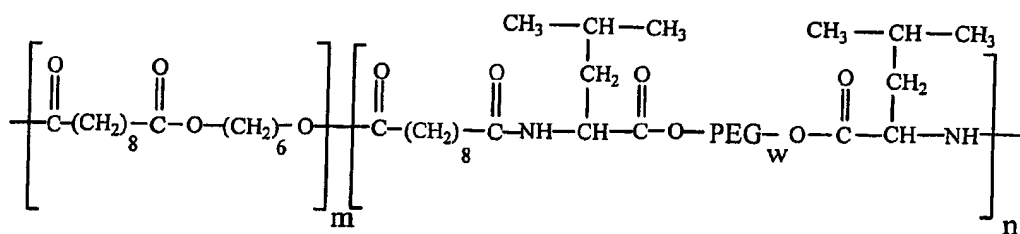
41. The method of Claim 40, wherein the copolymer is selected from a group consisting of copolymers of formulae (23), (24), (25), (26), (27), (28), (29), (30), (31), (32), (33), (34), (35), (36), (37), (38), (39), (40), (41), (42), and (43):



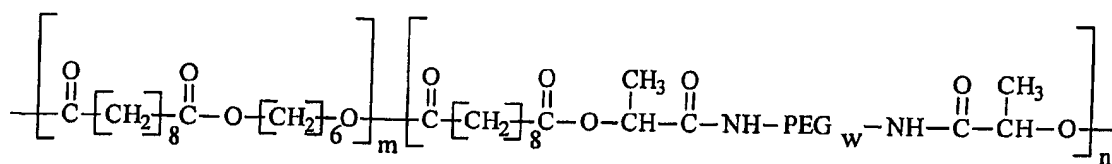



$$(30),$$


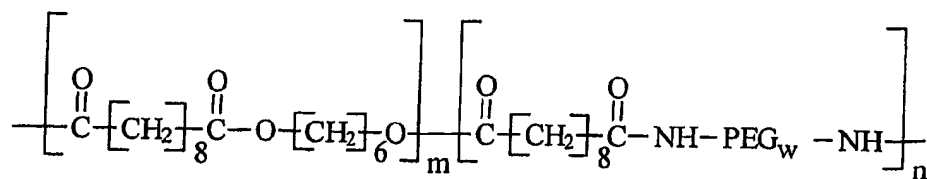
(31),



(32),

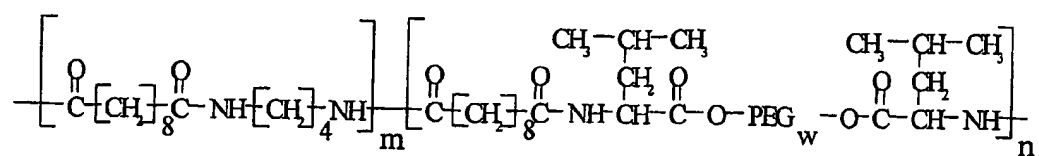


(33),

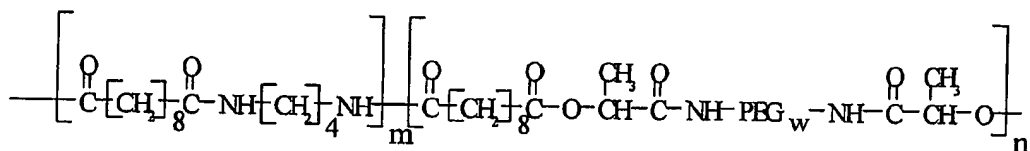


(34),

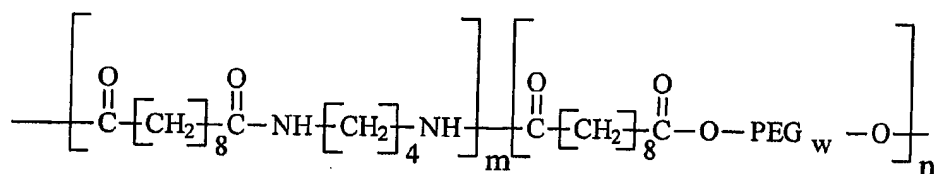




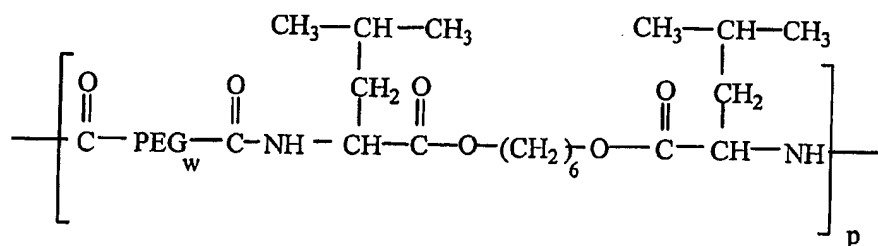
(35),



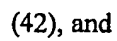
(36),

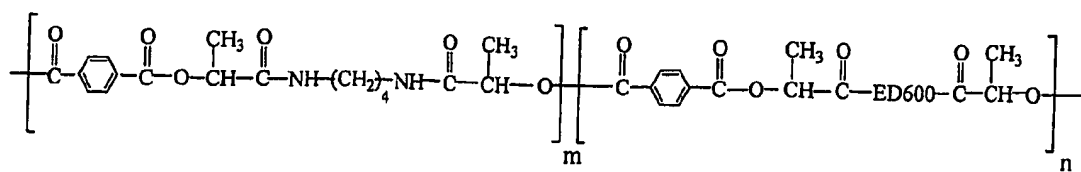


(37),



(38),





(43);

where m and n are integers, and w is a molecular weight ranging from about 100 to about 4,000 Daltons.